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May, 1937

The "Motor" Cortex. MARION HINES 313

A Curious Illustration of "Mass Reflex" and Involuntary Micturition Following Injury of the Spinal Cord. ORTHELLO R. LANGWORTHY 337

Cardiac Arrhythmia after Bilateral Ureteral Ligation in the Dog. WILLIAM M. NICHOLSON AND ABRAHAM J. SCHECHTER 346

On the Specificity of the Thyreotropic Action of the Anterior Pituitary Gland. KENDALL EMERSON, JR. 358

The Use of a Muscle Pedicle Flap for Prevention of Swelling of the Arm Following the Radical Operation for Carcinoma of the Breast. Preliminary Report. WILLIAM FRANCIS RIENHOFF, JR. 369

A New Operative Technique for Closure of the Main Bronchus. Preliminary Report. WILLIAM FRANCIS RIENHOFF, JR. 372

Book Reviews 374

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THE "MOTOR" CORTEX[1]

MARION HINES

From the Department of Anatomy, Johns Hopkins Medical School

Submitted for publication December 19, 1936

INTRODUCTION

You have generously invited me to come to Montreal for the purpose of discussing the motor cortex—one of those subjects in Neurology which for many years seemed emptied of further elucidation. Only a short time ago, I should have felt able to define the limits of the motor cortex and to describe in detail its contribution to movement. Today, I am not certain that I can define the term in a manner which would satisfy every one engaged in its study. What then is the "motor cortex"?

In his second Goulstonian Lecture (*British Medical Journal, March 6, 1869*) Hughlings Jackson said that "facts seem to show that the forepart of the brain serves in the motor aspect of mind, and we may fairly speculate that the posterior serves in the sensory." In other words, Jackson's line of division between the motor and the sensory cortices would be drawn in the depth of the central fissure. And at the present no one has had the temerity to gainsay the limits of this, its posterior boundary. The difference of opinion concerns the anterior boundary and is in part one of definition.

That part of the cortex cerebri which Jackson considered as serving "the motor aspect of the mind" is the frontal lobe. This lobe may be subdivided into two great regions, one lying anterior, the area frontalis granularis, and the other posterior, the area frontalis agranularis, in which, as its name indicates, the internal layer of granular cells (layer iv) is wanting.

These two large regions are subdivided into smaller ones, each characterized by its content of cell types and by the arrangement of

[1] Lecture given before the Montreal Neurological Society, December 9, 1936.

these cells in layers. These smaller areas were numbered by Brodmann (1906) and lettered by Economo and Koskinas (1925). The area frontalis agranularis is composed of two cytologically distinct regions, known as areas 4 and 6 or as FA and FB. In area 4, the fifth layer contains the giant pyramidal cells of Betz. But the lack of these cells of Betz in the homologous layer of area 6 is not its only distinction. A glance at the upper layers of FA and FB as photographed by Economo and Koskinas (1925) will show that the arrangement of cells in layer iii is, respectively, characteristic. And where between these two regions, area 4 and area 6, shall the anterior limit of the motor cortex be drawn? The position of this line will depend upon our definition of the "motor cortex."

The anterior limit of the motor field which has gained a certain general credence, crystallized by Leyton and Sherrington (1917), was determined by the results of stimulation with the faradic current. These authors were aware that the anterior border of the motor cortex so delimited transgressed Campbell's "precentral area," especially in its lower two-thirds, and lay therefore well within his "intermediate area." Foerster (1931), following the Vogts' work (1919) rather than that of the English school of physiologists, has allocated the "motor cortex" to area 4 itself; for he reports that the isolated movements of single segments of the extremities resulting from stimulation of the posterior border of area 6 (Vogts 6a) are no longer obtainable if an incision into the cortex has severed the transcortical fibers of the upper layers between areas 6 and 4, or if area 4 be destroyed, or the pyramidal tract be interrupted. Foerster's limitation of the "motor cortex" and the origin of the pyramidal tracts to area 4 would not be accepted by Walshe (1935). Walshe believes that "the hypothesis that the pyramidal tract derives solely within the area gigantopyramidalis [Brodmann's area 4] is as unfounded as that which identifies this area with the motor cortex of the physiologist" (p. 71). Further, Walshe considers that the term 'motor cortex' "is a physiological one and cannot be used to indicate either the precentral area, or that part of it known as the area gigantopyramidalis. It includes the entire precentral area and a considerable extent of the intermediate precentral area (Campbell)," p. 73. In other words, if I understand correctly, it is that region anterior to the central

fissure from which discrete movements can be elicited by stimulation with the faradic current.

This disagreement in precise delimitation of the "motor cortex" makes substitution of cyto-architectonically discrete regions necessary. For the last five years my colleagues and I have studied the development and function of the frontal lobe, especially the area frontalis agranularis, in the Macaca mulatta. I offer, then, for your consideration (1) the results of our analysis of the relation of this area to initiation and inhibition of movement and of its substrate, tone, and (2) a comparison of these results with certain of those which have been described for homologous conditions in man.

THE "MOTOR" CORTEX AS DETERMINED BY ELECTRICAL STIMULATION

Thus we may dismiss the definition of the "motor" cortex, although we are still faced with the necessity of attempting to distinguish the border between areas 4 and 6 if we are to compare the result of their respective ablations. No external morphology such as fissures or gyri proclaims this boundary. In my hands, as in those of Leyton and Sherrington, the faradic current delivered by the Harvard inductorium caused the anterior limit of the "motor" cortex to fall well within area 6. Since 1933 (Myers, 1936) we have used a sine wave current, whose strength and double vibrations per second can be calibrated and kept constant. Using a unipolar electrode of 0.6 mm. diameter mounted on a fine spring and using a strength of current near threshold value, the anterior border of the electro-excitable cortex producing isolated movements approaches that of the cyto-architectonically discrete area 4. Nevertheless, the border so delimited varied from animal to animal, and subsequent histological examination of this region revealed what might have been anticipated—a great variability in the site of its position. In general in the Macaca mulatta the position of the anterior boundary of area 4 approached that set by Brodmann (1906) for what he called *Cercopithecus campbellii* (Elliot's *Lasyopyga campbellii*) and by Mauss (1908) for *Cercopithecus fuliginosus* (Elliot's *Cercocebus aethiops*) rather than the Vogts' (1919) picture of Cercopithecus (species not given).

The use of the sine wave current did not change the broad outlines of the monkey's cortex as reported by Leyton and Sherrington, nor

change the old topographical localization of movements elicitable from the cortex, although it did enable us to establish with less overlap the horizontal lines separating the leg from the arm and the arm from the face. To Leyton and Sherrington's characteristics of motor cortex activity—facilitation, reversal and deviation of response,[2] Dr. Boynton (1933) added another, centripetal individuation, the reciprocal of facilitation.

Within the old topographical localization, we found (Boynton and Hines, unpublished) a certain tendency for isolated movements of distal parts to be localized in the posterior part of the precentral gyrus and those of the proximal parts to be localized in the anterior (abduction and adduction of the toes are exceptions). And in the cortices of fetal and baby macaques extension of distal parts was found to lie more posterior than flexion. Further, in young macaques, the threshold for effective stimuli is lower for the distal joints than for the proximal ones and higher for those points found anterior in the precental gyrus than for those nearer the central fissure. With this source of stimulus the isolated movements of certain individual

[2] Leyton and Sherrington (1917) found that the repetition of electrical stimulation of the same cortical "point" (*i.e.*, the area as large as the diameter of their monopolar electrode) did not always elicit similar movements. This "instability of cortical points" they believed to be an expression of transient physiological states, which made themselves felt as deviation of response, reversal of response, and facilitation. They defined *deviation of response* as the alteration of the character of the movement, such that movement of another joint or part appeared in place of the one which was originally elicited; *reversal of response*, as the alteration in "the sense of the movement" elicited, *i.e.*, the initial extension of the joint, became flexion; and *facilitation*, as the increase in amount of movement first elicited, with or without other modification (*i.e.*, slight flexion of the elbow becomes greater flexion of the elbow, with or without some other accompanying movement).

However, when one visualizes the anatomical structure of the cortex itself and realizes that upon stimulation of a single cortical "point", the electric current is being drawn through the animal to the area beneath the monopolar electrode, instability of the movement resulting from repeated stimulation should be expected. Nevertheless, if the general physiological state of the animal remain good and if the same electrical resistance of the animal be maintained, we have found it possible to elicit, after hours, a movement similar to the first elicited when the same cortical point is stimulated with the same cycle and the same voltage.

digits were obtained! And when this current was used to elicit movements from the cortices of mammals other than those of the Macaca mulatta, a certain cycle or a certain strength of stimulus could be found, which under ether would reproduce the timing, the sequence and the smoothness of the movement characteristic of the animal's normal movements. These were particularly evident when the cat (Boynton, unpublished) and the dog (Myers, unpublished) were compared with each other or with the monkey (Boynton, Straus and Hines, unpublished) or with the sloth (Straus and Hines, unpublished). Comparison in similar animals of the movements elicited by these two sources of current leaves no doubt in the mind of the observer that stimulation with the sine wave current elicits movements which approximate those seen in the unanaesthetized animal. And so far we have found that this stimulation of the precentral gyrus of the macaque elicits movements which resemble those elicited by the inductorium only when the muscles involved have been deafferented. Sherrington (1931) found that the response of deafferented muscle resembled that of the normal, but he was using for his source of energy the inductorium.

In our (Boynton, Straus and Hines) studies of the maturation of the precentral gyrus in fetal and young macaques, two general types of movements were elicited by the sine wave current (1) those which resembled the isolated movements of "motor" cortex stimulation and (2) those which did not. The earliest appearance of the "pyramidal type" of movement was found in a fetus of 135 days' gestation age.[3] The strength of current necessary to elicit isolated movement from the cortices of fetal and new-born macaques varied from about 1 to 5 m.a. The lower strengths were threshold values for movements of the digits and the points from which they were elicited lay posterior in the precentral gyrus. There was also a tendency for the three larger topographical areas (*i.e.* those of the face, the arm, and the leg) to be separated by a strip of cortical tissue from which no movement was elicited. Facilitation, reversal, deviation and centripetal in-

[3] The average period of gestation in the Macaca mulatta is 165 days. The fetal monkeys used in these experiments were given us by Dr. Carl Hartman of the Carnegie Laboratory of Embryology. The date of their conception was known; therefore their gestation age is not an estimate.

dividuation were present, but relatively undeveloped. Cortical points were unstable and easily fatigued when compared with those of the adult "motor" area. Some part of the conducting pathways found great difficulty in responding to double vibrations higher than 360 per second, in contrast to the year-old cortex which responded easily to those as high as 1450. The cycle which elicits movement at the least strength of current is 60 for the fetal and for the young macaque and 90 for four months or older. Projection of cortical maps of points from which certain movements were elicited made at the time of stimulation upon sections of the precentral gyrus of the cortex in question showed an extraordinarily close correspondence between the site of the anterior limit of electrical excitability determined in life and that of differentiation of the large pyramidal cells in layer V and of the maturation of the upper three layers of cells. The areas which were "silent" were relatively immature.

Therefore it is possible with the sine wave current to determine, more accurately than was anticipated from results with the inductorium, the borderline between areas 4 and 6. Then if the current used be kept within the threshold value, and a line be drawn through the anteriorly lying points from which isolated movements of the contralateral proximal parts of either the arm or the leg can be elicited, pieces of cortex removed from an individual brain anterior to this line will show themselves by examination of serial sections to contain cortical lamina characteristic of Brodmann's area 6 and those posterior, of Brodmann's area 4. Nevertheless, it is impossible to draw a picture of the brain of the adult Macaca mulatta and trace thereon an anterior boundary for area 4 which will hold true for all individuals of this species. A similar variation in the anterior extent of area 4 in man is indicated first by a comparison of the charts for man produced by the architectonic savants and secondly by the reports made by O'Leary to Sachs (1935) and of that made by Holmes (see Walshe, 1935) to Horsley (1909) for their respective removals of the precentral gyri.

RESULTS OF DIFFERENTIAL ABLATION OF THE AREA FRONTALIS AGRANULARIS

In man, ablation of, or injury to, the motor cortex and its projection pathways presents two diverse elements, paralysis and spasticity.

The paralysis is selective, choosing, for impairment or loss of voluntary movement, all skilled and isolated movements of the hand and fingers, extension of the proximal joints of the arm and flexion of those of the leg. The spasticity (Walshe, 1929) includes three phenomena which resemble somewhat in quality but not in distribution those which characterize the phenomena of release[4] in decerebrate rigidity. These three phenomena of release are muscular hypertonus, clonus and brisk tendon reflexes.

(a) Ablation of the Anterior Portion of Area 4—The "Strip" Area

In the rhesus monkey, these phenomena of release can be produced with minimal residual paralysis by a simple ablation of a slender strip in the anterior part of the "motor" cortex. Immediately after the operation, phenomena both of release and of paralysis appear in the extremities opposite the lesion. However, the impairment or loss of voluntary movement gradually regresses, so that two weeks after the operation the only residuum is the difficulty of adduction of the thigh and inability to spread the toes. But the phenomena of release remain.

The muscular hypertonus is differential in its distribution. In the limbs opposite the lesion it is maximal in the flexors of the elbow, in the extensors of the knee and in the adductors of the thigh. Consequently, resistance to passive movement is greater to extension at the elbow than to flexion, to flexion at the knee than to extension, to abduction of the thigh than to adduction. The quality of this resistance is known to the clinician as "the clasp knife phenomenon."

[4] This dual concept of the result of lesions of the central nervous system will be found in Hughlings Jackson's discussion of "Evolution and Dissolution of the Nervous System" (reprinted in vol. II, pp. 3 to 92 of Selected Writings). Jackson considered that the "process of dissolution is not only 'a taking off' of the higher, but is at the very same time a 'letting go' of the lower". Not only were certain normal functions lost, but also other functions were released, due he believed not to any direct pathological process but rather to the loss of control of lower levels by higher levels.

Consequently, in spastic hemiplegia in man, the functions lost are the most voluntary and skilled movements of the extremities opposite the lesion, and those released (the phenomena of release, Walshe, 1929) are the hypertonus, the clonus, the briskness of the tendon reflexes, the exaggeration of reflexes of muscular and labyrinthian origin, the so-called associated movements and the positive Babinski.

It is most easily demonstrated by stretching the extensors of the knee, but it is also present in all the muscles resisting passive movement. The first few degrees of flexion of the extended knee meets with no resistance, then through the next 30 degrees or more the resistance is great indeed and then it suddenly disappears. This example of Sherrington's lengthening reaction appears in several other guises. If, for example, a flexed elbow be passively extended in narrow arcs of movement with a short time interval between, the muscle tends to maintain each new length superimposed upon it and to resist the next arc of movement.

Further, these animals show an increase in the positive supporting reaction. Made to support the body either by the arms or the legs, the supporting extremities tend to extend and can be made to come gradually out into full extension by pressure transmitted through the pelvic or pectoral girdle; for, as the pressure is released, the extremity takes up a new position of greater extension until the extremities so tested are in full extension. Or, if the hand of the observer be placed under either the foot or the hand of the monkey and slight pressure upward be exerted, the leg or arm so tested extends and in some cases the extension is so rigid that the animal is carried upward for the distance of a foot or more before the knee or elbow flexes.

The second phenomenon of release is clonus, a rhythmic alternating predominance of excitation and inhibition, produced as a response to sudden and maintained stretch. Clonus is easily elicited opposite the lesion in muscles of the leg such as the quadriceps femoris, the gastrocnemius-soleus group, the adductors of the thigh, the tibialis anterior, the peroneus longus and the flexors of the toes. And in the arm, clonus is most often found in the biceps brachii and in the long flexors of the fingers and of the wrist and rarely in the triceps brachii. Also clonus may appear in any one or in all muscles involved in a given voluntary movement if the effort be great, or if the necessary response in the movement be sudden.

The third release phenomenon is that of brisk tendon reflexes, which irradiate to muscles not stimulated with the reflex hammer. Briskness is always a quality of the tendon jerks opposite the lesion if sufficient relaxation be secured. It is most easily observed as a characteristic response by the m. quadriceps femoris and by both the medial and

lateral groups of thigh flexors. Next in order of briskness are the tendon reflexes of the fingers and the toes, of the ankle, the long flexors of the forearm and the triceps and biceps brachii. Irradiation always involves muscles proximal to the one stimulated. Contraction in the m. quadriceps femoris is often accompanied by a strong contraction of the adductors of the same or of the opposite thigh. The tendon reflex of the ankle causes contraction not only of the gastrocnemius-soleus group but also of all the flexors of the thigh. The tendon reflexes of the digits may spread to all the flexors of the

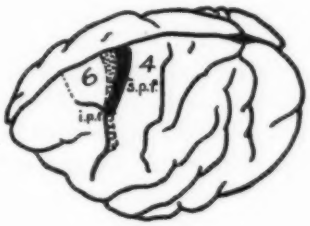

FIG. 1. The solid black area which passes through the superior precentral fissure (s. p. f.) extends from the inferior precentral fissure (i. p. f.) over the crest to the fissura calloso-marginalis on the medial surface. This region is the anterior border of Brodmann's area 4 and has been familarly called in this paper, the "strip" area. The stippled area lying anterior to the "strip" area is sometimes area 4 and sometimes area 6. In the report in this paper of an additional lesion anterior to that of removal of the "strip" area the whole of the stippled area was Brodmann's area 4, as well as the stippled area posterior to the transverse curve of the inferior precentral fissure in the precentral gyrus.

extremity concerned. And sometimes a contraction of the m. biceps brachii will spread to the adductors of the shoulder girdle.

The lesion (fig. 1) which produces these results is about 3 mm. in width. It passes through the superior precentral fissure. It extends from the inferior precentral fissure to the fissura callosomarginalis on the medial surface, following throughout at equidistance the curve of the central fissure. Certain additions to this lesion extend the distribution of the release phenomena without affecting in any way either the initial or the residual paralysis. The extension of the above lesion to include also (1) the whole of the anterior border of the motor

cortex which lies dorsal to the inferior precentral gyrus or to include (2) the anterior border of the face area produces, in addition to the contralateral release, a similar shortlived release in the extremities of the ipsilateral side. On the other hand, incomplete removal of the strip of cortical tissue passing through the superior precentral fissure is followed by a transient appearance of some or of all of these phenomena of release in both the contralateral limbs without topographical localization. Thus, twenty-four hours after the removal of the lower half of this strip of tissue (anterior to the arm area only) paralysis was limited to the inability to protract and to adduct the contralateral arm, but the phenomena of release are present alike in the opposite arm and leg.

Furthermore, if one medial surface of this strip of cortical tissue be preserved, the phenomena of release will be transient. Subsequent removal of this one medial surface reproduced all of the phenomena in all four extremities, stronger on the ipsilateral side. Complete bilateral removals produce apparently permanent results (8 mos.). These operations demonstrate therefore that in the anterior part of the monkey's cortex at least two projection systems must exist, one which initiates isolated discrete movements, the other, which inhibits the appearance of hypertonus, clonus and brisk irradiating reflexes. The paralysis produced by the loss of the former is contralateral and topographical in its distribution and the release phenomena resulting from injury to the latter are bilateral although dominantly contralateral in their distribution and show no evidence of topographical localization.

(*b*) *Ablation of Area 6*

On the other hand, ablation of Brodmann's area 6[5] is not followed (1) by a single sign of paralysis, (2) nor by a single sign of any one of

[5] It is obvious that these results do not conform to those which Fulton and his collaborators have described following removal of the premotor area of Campbell or area 6 of Brodmann. In 1932 Fulton *et al.*, (p. 534) summarized the results of lesions of the premotor area as obviously affecting the postural mechanism, but as not leading to pronounced hypertonia. In 1934 Fulton says that "persisting indefinitely in experimental animals, spasticity and the associated increase of tendon reflexes must also be regarded as a distinctive manifestation of a premotor lesion. Motor lesions, on the other hand, especially if acute, give

these phenomena of release. Rather, the phenomenon which invariably follows removal of area 6 dorsal to the anterior curve of the inferior precentral fissure is that of the grasp reflex. This reflex tested by the best clinical methods has a certain permanence. It is in reality an inability to relax a flexion of the fingers produced initially by pressure on the interdigital pads and maintained by stretch upon the flexors of the fingers. If the stimulus afforded by stretching be relaxed, the monkey can easily extend the fingers. This reflex shows a certain topographical preference—it is always better developed and more permanent in the hands than in the feet. The grasp reflex produced in the hand opposite the operation disappears shortly after unilateral ablations and becomes permanent (about a year) only after bilateral removal. The systems (or system) here removed are clearly extrapyramidal and also are apparently bilateral, stronger in their ability to inhibit flexion on the contralateral side.

(c) *Combined Ablation of the "Strip" Area and Area 6*

A combination of these two lesions changes materially the clinical picture of either of them. And whatever the order of operation, a certain similar residual symptomatology appears with time. The addition of area 6 to the anterior border of area 4 causes a loss of the clasp-knife type of differential resistance to passive movement. Resistance to passive movement is present but similar in protagonists and antagonists in the proximal joints of all four extremities. Brisk irradiating reflexes gradually subside. Clonus easily elicited distally remained for a year. Now, a year and a half after the last operation,

---

rise to depression of reflexes and generally to flaccid paralysis" (p. 12). These apparently contradictory results can be explained when the outlines of the respective lesions are compared. In the first paper, the outline of the region removed conformed fairly closely to Brodmann's area 6; in the second there was apparent inclusion within the field of operation of the anterior border of area 4. This second operation resembles those reported in this lecture as the combination of ablation of Brodmann's area 6, and of the anterior border of area 4. The second lesion of Fulton followed the outline of area 6 as pictured by the Vogts (1919) for *Cercopithecus* (species not given). In the Macaca mulatta however area 4 extends further forward than the Vogts reported it for *Cercopithecus*, and resembles, as Brodmann himself said, the condition which he pictured for *Cercopithecus campbellii* (1906, p. 317, figs. 76 & 77).

quick movements in a large cage are accompanied by tremors of the flexors of the thigh, visible at appreciable distance. The grasp reflex appeared in the hand opposite each new lesion in turn and was demonstrated to be present in both hands six weeks after the last lesion.

If the order of these operations be reversed, resistance to passive movement appears similar in protagonists and antagonists, but is not clasp knife in quality. Brisk irradiating reflexes appear, and gradually disappear. Clonus appeared and remained for almost a year. The grasp reflex disappeared gradually. But the most startling phenomenon was a rigidity of extension produced by standing, which gradually subsided during the eleven months after the last operation.

So far these experimental ablations demonstrate that the anterior part of area 4 contains projection systems which inhibit tonic extension, and area 6, those which inhibit the grasp, containing perhaps the frontal lobe's contribution to a reciprocal inhibition of tonic states in muscle.

(*d*) *Ablation of the Whole of Area 4 or Its Posterior Portion*

But the results of large lesions of area 4, either of the whole or the posterior part of area 4 are in marked contrast to those of only the anterior part of area 4. In the latter group the phenomena of release take precedence over those of paralysis; while in the former, the reverse is the case. In neither was the paralysis following these lesions flaccid in the sense that the extremities opposite the lesion were limp. Following the ablation of the posterior half of area 4 (*i.e.* posterior to the "strip" area including the arm and leg areas but sparing the face), the rather complete paralysis disappeared after two days, that of slight residual impairment in two months. Nevertheless, the phenomena of release (as increase in resistance to passive movement and brisk tendon reflexes) were difficult to demonstrate.[6] Clonus was not observed. Certainly a contrast to the sequelae of strip lesions or to those of total area 4; for after removal of total area 4, the limbs opposite the lesion were not used to initiate independent movement. They aided or followed movements of the other extremities. All of the digits of the

[6] The results of removal of the posterior part of area 4 seem to resemble those described by Fulton and Kennard (1932) as sequelae of their "motor area preparations" (pp. 162–165).

hand were moved simultaneously. In struggling, these limbs shot out into extension at the distal joints, the digits were extended and maximally abducted. All three phenomena of release were present. The tendon reflexes passed through a pendular stage before they became brisk and irradiating. Clonus was present for four months. The differential resistance to passive movement with the exception of that to abduction of the thigh developed slowly with time, but the hypertonus never became as great as that found opposite "strip" lesions.

In all animals, whose lesions include any part of the anterior border of area 4, a steady resistance develops to dorso-flexion of the wrist and ankle opposite the lesion. This resistance is associated with the gradual development of a shortening in the flexors of the joint concerned. A similar shortening is also found in the flexors of the elbow and those of the knee. So far, I have not observed that any increase of resistance is associated with the shortening of the flexors of the knee. At some position in the arc of extension the flexors stop lengthening and refuse to allow any further extension of the knee. These shortenings resemble the contractures described for man in spastic paralysis. If the lesion be restricted to the "strip," these contractures are slight. The addition of area 6 does not apparently increase them, but does not prevent their appearance. But if to the strip be added (1), a further encroachment upon area 4, contracture is great and develops in the second or third month or (2) all the remaining area 4 (except the face area), the shortening is eventually of a greater degree and definitely postponed. If, on the other hand, the lesion be restricted to the posterior part of area 4, shortening is less than that found after lesions of the anterior part of 4. It is greatly postponed in its appearance and is confined to the flexors of the wrist and of the ankle. The lesions described in this paper have not been followed by shortening of the long flexors of the fingers. In my experience permanent shortening of these muscles follows only bilateral removals of areas 4 and 6 or of the frontal lobe.

SURGICAL DIVISION OF THE PYRAMIDS

These findings can be elucidated by comparing them (1) to those which Dr. Tower has observed to characterize the macaque following

section of one pyramid,[7] and (2) to those which are elicited by electrical stimulation of the cortex cerebri after acute section of both pyramids.

The results of cutting a pyramid, as described by Dr. Tower, are in marked contrast to those of differential ablations of area 4. Following a lesion of one pyramid, the initiation of isolated "purposive" movements vanishes. The extremities opposite the lesion are used only as aids to the normal extremities. No self examination, no taking of preferred food by either the hand or the foot, have ever been observed. The fingers can grasp and hold the mesh of the cage in climbing, but the toes do not. These digits are placed in extension flat against the mesh. The contralateral shoulder droops in sitting, the arm is held in adduction at the shoulder and flexion at the elbow, the thigh is adducted and the lower leg is abducted. In walking the animal rests briefly on these extremities and in the step forward the leg is raised high and thrown forwards.

At no time following such a lesion (22 mos. at present writing) has any muscle or group of muscles shown an increase in resistance to passive movement. In fact no muscle opposite the lesion escapes a certain degree of hypotonia. Consequently, the tendon reflexes present opposite the lesion are not brisk and active and the excursions produced are not damped by their antagonists. The tendon reflex of the toes was never observed.

Clonus was never elicited nor observed on the side affected by the lesion. Nevertheless, in movements of violent activity, the contractions of the extensors of the limbs were never fused into smooth movements. The limb shot out in a jerky fashion. And as a part of this picture an accentuated emotional state always increased tone in all muscles which responded in movement to an expression of that state. A similar state was observed also in the limbs opposite complete area-4 lesions.

In contrast to the contracture or shortening of length to which a muscle may be stretched, described for lesions of area 4, those of the

[7] This operation for the macaque was described by Dr. Tower at the 1935 International Neurological Congress, London. For the cat, report of similar, and at the present time, more complete studies will be found in *Brain*, 1935, vol. 58. p. 238, and 1936, vol. 59, p. 408.

extremities opposite a severed pyramid atrophied. And the wasting was greater in the leg than in the arm.

Therefore, the paralysis of the extremities following cutting of a pyramid resembles that which follows the ablation of all of area 4 above the face region. But, the unilateral pyramidal preparation is hypotonic. It shows none of these so-called signs of spasticity. Apparently, there remains in the cortex, in spite of the loss of the cortico-spinal tract, some type of projection system which acts as an inhibitor of these particular tonic muscular reactions.

That these differential ablations remove two apparently different groups of inhibitors can be shown by another type of investigation. Stimulation of the area frontalis agranularis after acute section of the pyramids (Tower and Hines, 1935) in the Macaca mulatta supports the belief that in the absence of the cortico-spinal tract, the projection systems which remain (and they are clearly extrapyramidal) show a certain grouping in this part of the cortex in respect to the types of tonicity which they inhibit and the kind of movement which they initiate. This grouping, as indicated by the results of stimulation of this part of the cortex, is not topographical. The initiation of patterns of movement with grasping is associated spacially in the cortex with relaxation of the grasp; and initiation of diagonal patterns, postural or progression, with inhibition of tonic extension.

The former group, that of the production of patterns with grasping and relaxation of the grasp, are fairly well localized in the anterior part of the area frontalis agranularis, Brodmann's area 6. The latter group, that of the production of postural and progressive diagonal patterns and inhibition of tonic extension, is more concentrated in the anterior half of area 4 than in its posterior half. The effects of stimulation of these cortical areas are greater contralaterally than ipsilaterally. And in the case of inhibition of tonic extension, the ipsilateral effect is generally found anterior in the cortex to that of the contralateral effect.

Up to the present time the stimulation of the posterior part of area 4 has yielded little in the way of inhibition of tone either in general or in particular. It is not impossible that this region of the cortex suffers a retrograde shock in acute division of the pyramids. Nevertheless, the result of ablation of the whole posterior division of area

4 was also marked by the absence of any but the slightest evidence of the removal of cortical inhibition. So that in this particular region, as elsewhere in the area frontalis agranularis, the results of its stimulation after pyramidal section are to those of differential ablation as a slightly distorted mirror image. The removal of the anterior division of area 4 (the "strip" area) gave a maximum loss of inhibition of extension; its stimulation, relaxation of tonic extension. The removal of area 6 gave the grasp reflex; its stimulation, relaxation of tonic flexion including the grasp. The removal of both of these areas resulted in the release of two opposing inhibitions which tend to neutralize each other, such that differential resistance to passive movement is lost; and resistance becomes distributed equally between protagonists and antagonists.

FETAL DEVELOPMENT OF PROJECTION PATHWAYS FROM THE AREA FRONTALIS AGRANULARIS

A careful consideration of the results of these experimental lesions and of these stimulations of the monkey's cortex, after division of the pyramids, indicates that paralysis of isolated movements might be allocated to the loss of the pyramidal tract and that the findings, grouped as spasticity, to the removal of extrapyramidal projection pathways. If this conclusion be true, then our series of stimulations of the cortices of fetal monkeys should uncover activity which cannot be allocated to that of the pyramidal tract. And they did!

Isolated movements such as adduction of the hallux or of the thumb, extension of the fingers and movements of the tongue, were elicited by stimulation of points in the posterior part of the precentral gyrus of a fetal monkey, removed after 135 days' gestation (*i.e.*, 30 days before birth). Stimulation of this same region was able to relax the position of the extremities and to quiet spontaneous movement. Stimulation of the anterior division of area 4, from which no isolated movements were elicited, relaxed tonic extension in the crossed extremities. But stimulation of area 6 was never observed to relax the grasp or to produce any patterns of movement with grasping.

Two fetal monkeys, whose cortices were explored aseptically with the sine wave current immediately after their removal by Caesarian section, were kept alive. On the following day their pyramids were

cut by Dr. Tower and their cortices re-explored. In the younger fetus (147 days' gestation age) no trace of extrapyramidal motor activity was observed, while in the older one (162 days' gestation age) a trace only was present. Stimulation of area 6 produced relaxation of flexion of the proximal joints of both extremities without any effect upon the grasp. In both of these fetuses relaxation of induced flexion of the extremities and cessation of movement were obtained by stimulation of the precentral gyrus. But in each of them the "strip" area was relatively inactive as compared with that of the adult, although isolated observations demonstrated that relaxation of extension of the extremities, even of the fingers, was present in the anterior part of area 4.

These incomplete studies indicate that the group of extrapyramidal effects demonstrated for the area frontalis agranularis of the adult macaque's cortex develop differentially. Adversive movements of the trunk and limbs, conjugate deviation of the eyes, diagonal patterns and patterns with grasping, have not been observed in fetal monkeys. Relaxation of flexion of proximal joints in the older two was apparently better developed than relaxation of extension. But relaxation of the grasp was not observed. And in the 135-day fetus stimulation of area 4 produced relaxation where no movements of the pyramidal type were elicited. Is it unjustifiable to conclude that extrapyramidal inhibition develops before pyramidal activity and that extrapyramidal inhibition and pyramidal initiation influence the motor cells of the spinal cord over different pathways? The human newborn is not spastic in spite of its positive Babinski!

SPASTIC PARALYSIS IN MAN

In what respects do the paralysis and spasticity produced in the Macaca mulatta resemble or differ from the symptom complex of spastic paralysis in man? In the macaque two types of lesions were used to produce paralysis—removal of area 4 and section of the pyramids. Taking into account the relative skill in the use of muscles by the monkey and by man, each of these two operations produced a loss of isolated voluntary movements which approaches the loss suffered by man after lesions of his motor cortex. Foerster (1936) reports that, after ablation of the lower arm area, the patient could

close and open the hand, but could not flex or extend a single finger or a single segment. And after years of training he was never able to oppose the left thumb unaccompanied by a similar opposition in the normal hand. In the monkey, a year and a half after pyramidal section, the thumb was observed to be used opposed to all of the fingers.

The distribution of maximal paralysis is similar in both the unilateral pyramidal preparations and in those of ablation of the arm and leg regions of area 4. But that resulting from section of a pyramid is easier to observe over long periods of time because the phenomena associated with spasticity are absent. A comparison of the distribution of maximal paralysis in man, as observed by the savants of clinical neurology, with those which we have seen in either of these experimental lesions in the macaque show an astounding similarity. And I am certain you will recognize in this list that the homologous muscles of man are those maximally paralyzed in the macaque—the proximal flexors of the leg, the adductors of the thigh, the dorso-flexors of the foot and the flexors of the toes; the extensors of the elbow, wrist and fingers, the abductors and elevators of the shoulder and the supinator of the forearm.

The selective distribution of increase in resistance to passive movement of the clasp knife type described for man was similar to that found in the monkey. In both this type of resistance characteristic of spasticity was found in the extensors of the knee and in the flexors of the elbow. But if the monkey were made to support the weight of his body on his arm, this type of resistance seemed to shift to the extensors. This finding resembles a condition in certain human hemiplegics which Brain (1927) has called the quadrupedal extensor reflex.

If on the other hand the selective distribution of hypertonus and that of maximal shortening of muscles be compared, a greater divergence will be observed. In the macaque, lesions of area 4 involving its anterior border did not produce any increase of resistance to passive movement in the muscles of the digits, or of the adductors of the shoulder or of the pronators of the forearm. The picture of differential distribution of maximal shortening is so dissimilar to that found in man that the hemiplegic picture of contracture is only partially approached. Lesions of area 4 did not produce any shortening of the

muscles of either the fingers or the toes. In the arm the flexors of the elbow and of the wrist, and in the leg the flexors of the ankle, are shortened as in man; but unlike those of man, in the macaque the flexors, rather than the extensors of the knee, show contracture. A bilateral long-standing ablation of the area frontalis agranularis (the face area of the "motor" cortex was not removed) reproduced the hemiplegic posture of contracture in the arm but not in the leg. But to this picture were added permanent elevation of the shoulder and a rigid abdomen. At the present I know of no operation on the macaque which will cause contracture of the muscles of the foot and toes.

In the recent studies of the results either of ablation of the "motor" cortex or of cerebral accidents producing spastic paralysis in man, the symptom complex of both the hypertonicity and the paralysis are described as found on the side opposite the lesion. But in the monkey certain lesions were described which did produce increased resistance to passive movement, clonus and brisk irradiating reflexes (1) on the side of the lesion and (2) in muscles in which no paralysis had been observed. Is this distribution of release phenomena peculiar to the monkey? The older clinical literature answers this question in the negative. Dejerine (1909) thought that the extremities on the side of the lesion sometimes present a certain degree of participation in the spastic state. The tendon reflexes were described as bilaterally modified (Brissaud, 1880; Dignat, 1883) and clonus was present on both sides in cases of unilateral hemiplegia (Westphal, 1875; Dejerine, 1878; Dignat, 1883). And Bergmark (1909) reported a case (No. 23) of monoplegia in which the leg was apparently not paretic, and "the finer motility of the hand" was almost completely restored. The tendon reflexes were greatly increased in the proximal joints of the leg and in the distal joints of the arm or in the parts of the arm which had become relatively free from paralysis.

This appearance of certain of the signs of spasticity in non-paralyzed parts is rare in man. And of course it is not impossible that I have happened upon the rarer cases first, in my ablations of area 4 in the monkey. Nevertheless, in the monkey, comparison of the results of ablation of the anterior part of area 4 with those of unilateral pyramidal section and a consideration of the relative development of inhibition and initiation of movement in the cortex of fetal

monkeys make the postulation of separate pathways almost inevitable. Is there then any other evidence which can be presented which points to similar conclusions for man?

Spielmeyer (1906), Hoerstermann (1912) and Bielschowsky (1916) have reported cases in which spastic paralysis was present in spite of anatomically intact pyramidal tracts. All of these cases, however, have one common serious flaw; in life these individuals were idiots. But Finkelnburg's (1913) patient was not. The clinical diagnosis was congenital spastic paraplegia, and death came from tuberculosis of the lungs. Finkelnburg examined microscopically both central gyri, part of the frontal and of the occipital lobes, the internal capsule, pons, medulla oblongata, and the spinal cord. Throughout the pyramidal tracts were morphologically intact. The sections of the cortex other than the precentral gyrus showed no atrophy. The cells of the outer layers of the "motor" cortex were greatly reduced in number and arranged with great irregularity. The cell contents of the fifth layer almost approached the normal, with only occasional losses of cells. The giant pyramidal cells seemed to approach the normal number. But, because no stains for fibers were used on the "motor" cortex we do not know whether or not the pyramidal cells of Betz were anatomically intact and functionally isolated. And were they not, the presence of the spasticity would modify greatly all voluntary movements. On the other hand, Bergmark (1909) has found a few cases of paralysis of cortical origin, unaccompanied by signs of spasticity. Had this evidence been in the hands of the clinical neurologists forty years ago, I doubt whether they would have attempted to allocate the loss of inhibition and of initiation of movement to loss of a single descending system, and perhaps would have suggested with Walshe (1919) that a typical spastic hemiplegia may ultimately reveal a component other than the cortico-spinal system.

Chance only occasionally produces lesions which isolate paralysis and spasticity in man. Nevertheless, comparison of the results of removal of the hand area (Foerster, 1936) with those of the arm area (Horsley, 1909) seems to indicate that the larger ablation removes a greater proportion of projection systems which prevent the appearance of subsequent shortening of muscle. Such evidence is not con-

clusive, but worth consideration; for it is possible that the extrapyramidal inhibitors are more concentrated in the motor cortex of man, and as in the monkey, possess a certain mass effect upon lower centers.

GENERAL DISCUSSION

So far, the results of our analysis of the area frontalis agranularis of the cortex in the Macaca mulatta indicate that its projection fibers can be grouped as pyramidal and extrapyramidal. The removal of the pyramidal system alone leaves the extrapyramidal in full activity, with the result that isolated voluntary movements of discrete parts are maximally lost, together with a marked decrement in the normal tone of all muscles. This hypotonia decreases with time in certain muscles so that maximal paralysis follows closely that described for man. But the phenomena of release in the form of spasticity did not appear.

The extrapyramidal projection systems can be classed as those which initiate movements and those which inhibit both movement and tonic states. Certain of these inhibitory mechanisms for movement and for tonic states have been demonstrated to develop before either those which initiate synergic movements, or those which initiate voluntary movements. The initiation of movements predominately flexor in type, and the inhibition of tonic flexor states, are concentrated in area 6, the region whose removal produces the grasp reflex in the monkey. The initiation of diagonal movements and the inhibition of tonic extensor states are concentrated posteriorly to area 6 in the anterior border of area 4. Removal of this region produces a marked extension especially of the legs, which is difficult for the animal in life to inhibit. Besides this striking result, three phenomena of release appear that resemble spasticity in man's spastic paralysis. Ablation of each of these areas in sequence produces an animal which reminds one of the "tonic innervation" of Wilson and Walshe (1914). Ablation of area 4 resembles in the paralysis which it produces that of unilateral division of the pyramids but in addition shows certain signs of spasticity.

In conclusion we would allocate paralysis to interruption of the cortico-spinal tract and spasticity to that of extrapyramidal systems

closely associated in cortical space. The distribution of paralysis which followed lesions of area 4 demonstrates once again the topographical localization of movements in the motor cortex.

But so far, we have no evidence for such a localization either of the inhibitors of tonic states or of their associated movements. Rather these inhibitors are grouped physiologically, so that those of flexor tone lie anteriorly to those of extensor tone and affect both the arm and the leg in a similar manner. Between them they produce a certain reciprocal inhibition which lends easy initiation to all voluntary movement.

And although I have not defined the motor cortex as such, it is clear that, when certain precautions are taken, movements which have been previously described as characteristic of the "motor" cortex can be allocated to Brodmann's area 4.

Therefore, in the rhesus monkey it is possible by differential lesions of area 4 (1) to separate for isolated study certain of the phenomena of release characteristic of man's spastic paralysis; (2) to complicate this picture by adding to it greater impairment of voluntary movement and definite contractures and (3) by cutting the pyramids, to produce paralysis without any of these signs of spasticity. We have been able then to separate the phenomena of spasticity from its companion paralysis and to demonstrate for your consideration a new localization for the inhibition of that substrate of movement, tone.

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A CURIOUS ILLUSTRATION OF "MASS REFLEX" AND INVOLUNTARY MICTURITION FOLLOWING INJURY OF THE SPINAL CORD

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INTRODUCTION

This case is reported because of the demonstration of the so-called "mass reflex," and particularly as an illustration of the "sacral reflex" described by Denny-Brown and Robertson (1933). It offers a clinical example of the influence of peripheral stimuli upon micturition and supplements our experimental observations upon cats after transection of the spinal cord in the lower lumbar region (Langworthy and Hesser, 1937).

Head and Riddoch (1917) studied vesical activity in young adult males with transection of the spinal cord due to war wounds. After the period of shock which followed the accident had passed away, the portion of the body controlled by the isolated section of the spinal cord often became reflexly very active. Involuntary flexor spasms of the legs occurred. Mere stimulation of the sole of the foot caused flexion of the legs, sweating, and evacuation of the bowels and bladder. Sex reflexes consisting of erection and emission could also be obtained. The widespread response to stimulation was called a "mass reflex," inasmuch as Head and Riddoch thought that sensory stimuli spread widely to all motor cells of the isolated cord. Micturition under these circumstances was attributed to a vast outburst of motor energy overflowing into visceral channels, or a wide irradiation of the reflexes due to loss of "local signature." These authors further concluded that the responses of flexion of the legs, sweating, micturition and defecation were all manifestations of a primitive defense reflex.

Walshe (1921) questioned this interpretation in terms of a defense reflex. "Rather the activity represents reflex anarchy serving no

useful purpose." The interpretation of abnormal neurological findings in terms of the release of more primitive reflex mechanisms is to him inadmissible.

Holmes (1933) observed that the reflex micturition associated with flexion of the legs in these cases was not the immediate result of stimulation of the legs but had a definite latent period. He concluded that it was dependent on the associated, forceful contraction of the abdominal wall, and that this increased the intra-abdominal pressure and the tension on the bladder, stimulating the hyper-irritable vesical musculature to contraction. There was an interval, sometimes of several seconds, between the flexion of the legs and the onset of micturition. In cases in which the lesion was so low in the cord that the reflexes excited in the legs did not spread to the abdominal muscles, stimulation of the soles of the feet had no effect upon the bladder.

Denny-Brown and Robertson (1933) considered that the so-called "mass reflex" could be subdivided into a number of more purposeful responses. The striated muscle of the external sphincters contracted along with the flexor muscles of the legs in response to stimulation of the sole of the foot. Not only was micturition not immediately associated with flexion of the legs, but micturition was invariably interrupted by stimulation of the foot due to the closure of the external sphincter. Closure of the external sphincter was followed by a decrease of vesical contraction. The effect upon the external sphincter was brief and micturition might be initiated or recommence after a latent period.

They found that contraction of the vesical muscle could be induced by stimulation of the skin supplied by the sacral segments of the cord. The contraction was smaller when elicited from the first and second sacral segments, and it was doubtful whether it could be obtained at all from the skin innervated from the lumbar segments. Only from the sacral region was obtained a true reflex facilitation of micturition.

Denny-Brown and Robertson obtained from cutaneous stimulation of the sacral area further reflex activity which they called the sacral reflex. This included the anal reflex. Both thighs were slightly abducted and rotated outward, the perineum was vigorously retracted with contraction of the external anal sphincter, and the great

toe on each side was plantar flexed. The other toes were flexed slightly and were approximated.

In summary, contraction of the bladder muscle as a direct effect of cutaneous stimulation can be obtained only from the sacral area. Violent contraction of the abdominal wall may produce vesical contraction secondarily by direct stimulation of the bladder muscle. Cessation of vesical contraction follows reflex closure of the external sphincter. Head and Riddoch largely disregarded the part played by the external sphincter in the reflex control of micturition inasmuch as they studied the intravesical responses with a catheter in the bladder.

CASE REPORT

The patient (U 40, 118), a white married woman of 31, was well until August 1930 when her back was injured in an automobile accident. Paralysis of both legs developed and anesthesia as high as the mid-abdomen. X-ray of the spine is said to have shown a fracture of the first lumbar vertebra. She was kept in a cast for several weeks.

She was first seen in this hospital in November 1931. There had been a steady improvement in her condition, and motor power had returned at the hip and knees. There was little strength at the ankles. Sensory loss had become less marked. The patient was much constipated.

Neurological examination revealed a well developed and nourished woman of unusual intelligence and powers of observation. There was moderate wasting of the calf muscles, and the buttocks were soft and flabby. There was no spasticity on passive movement of the legs. Indeed muscle tone was greatly diminished at the ankle joints and perhaps in the extensors of the hip. At the hip, flexor power was strong, and extension only moderately weak. At the knee, extension was strong but flexion was slightly weak. At the ankle, power was greatly diminished, both flexion and extension being very feeble. The right ankle was weaker than the left. The toes of the right foot could scarcely be moved at all.

There was hypalgesia over the feet, ankles and lower one-third of the outer sides of both legs. This extended upward over the back of the calves and thighs and involved the inner surfaces of the buttocks. Touch was preserved but there was thermanesthesia corresponding with the area of hypalgesia. Sense of passive movement of the toes and vibratory sense were preserved. There was no tenderness of muscles or nerves.

The knee and hamstring jerks were very brisk; the ankle jerks were lost. No response to plantar stimulation of the feet could be elicited. The abdominals were active.

The patient walked with a broad base. The feet were raised high and slapped against the floor. The hips and body were rotated to advance the legs.

There was a small scar over the spinous process of the first lumbar vertebra, and under it a slight bony prominence could be felt.

A laminectomy was performed in 1931, and the arches of the twelfth thoracic and first and second lumbar vertebrae were removed. The dura was not opened. The patient was fitted with braces for her legs, and massage was continued. In 1934 she could walk a short distance without the aid of a cane. There had been little change in her condition.

A complete story of the disturbances of micturition was obtained in 1934. Following the accident, catheterization was required for 3 weeks; there was continuous dribbling of urine for 3 months before automatic micturition became established. Then urine was voided in small quantities at frequent intervals. The patient observed a sharp pain in the urethra just before automatic voiding occurred. This pain became more severe after the laminectomy.

A short time later she noticed that the right toes flexed and the foot inverted when the bladder was about to empty. This was accompanied by a cramp-like pain in the calf muscles. The toes remained in this position until toward the end of micturition when they slowly relaxed. The toes of the left foot showed a similar response but less marked. Cramping of the toes and the severe associated pain gave the only warning that micturition was imminent. The pain in the feet was always associated with muscle contraction. Stimulation over the area of diminished sensation on the buttocks brought on the contraction of the toes and the cramp-like pain, and sometimes induced micturition.

Bladder emptying was brought about in a number of different ways. First, the patient believed that there was a strong psychic factor. "I urinate whenever I go to see a new doctor." If a moving picture became exciting, the bladder emptied. When she rose from a chair and walked a few steps, micturition took place. This was apparently a response to stimulation of the soles of the feet.

In order to control micturition she attempted to empty the bladder every hour. Voiding was initiated by pulling the pubic hairs or by stimulation of the perineum and vagina. The stream had little force. The amount of urine passed at one time was 100 to 150 cc.

There were also means of postponing micturition. Pressure on the toes to keep them extended would delay vesical emptying, and she tried binding the toes in extension. The muscle contraction finally became very severe, and the bladder would empty. Pressure on the perineum or crossing the legs would also postpone emptying.

Reflex activity could be induced by stimulation over the inner surfaces of the buttocks. Painful stimuli on the right caused strong flexion of the right great toe, flexion of the other toes, flexion of the left great toe and adduction of the right foot. The legs were extended at the hip and internally rotated. Stimulation on the left gave a less marked response, usually beginning with flexion of the left great toe and then producing flexion of the toes on the right.

Normal sexual activity was impossible. Although the vagina was totally anesthetic, stimulation of the vagina particularly in the region of the clitoris produced the characteristic cramps and pains in the legs, and initiated micturition.

ANATOMICAL AND PHYSIOLOGICAL INTERPRETATION

It is difficult to visualize the anatomical lesion in this case. The complicated types of changes produced in the cord by trauma have been discussed by Holmes (1915). The responses of the bladder suggest those observed by Head and Riddoch (1917) after complete transverse section of the spinal cord. The crushing lesion must have injured the fourth lumbar segment of the spinal cord, and produced secondary injury responsible for transient anesthesia and paralysis to the level of the umbilicus. The latter gradually disappeared leaving only the manifestations of cord damage to the lower lumbar segments.

Clearly there was not a total transverse section of the spinal cord. Vibratory and sense of passive movement were preserved in the legs, suggesting that the posterior columns were intact. There was loss of pain and temperature sensation over the portions of the body supplied by the fifth lumbar and all the sacral segments. Tactile sensation was preserved. The pain-temperature fibers lie in the ventral columns of the cord. Tactile fibers run both in the ventral and posterior columns, and for this reason touch was preserved. There is little objective evidence of cortico-spinal tract injury. A positive Babinski could not be obtained owing to loss of pain sensation over the dorsal surface of the feet. The deep tendon reflexes of the quadratus and hamstring muscles were hyperactive. The behavior of the bladder suggests injury to the ventro-lateral columns of the cord including some damage to the cortico-spinal pathways.

Bladder distention and impending micturition could be recognized only by the cramping of the leg muscles. The sensory pathways carrying normal recognition of the bladder distention were destroyed. Barrington (1933) has shown that these pathways lie in the lateral columns of the cord, and our own experiments tend to confirm this finding (Dees and Langworthy, 1935).

The patient noticed responses of the bladder to emotional stimuli. These are often marked in patients with hyper-irritable bladders due

to partial damage of the efferent pathways from the brain which control the vesical muscle. Waves of bladder contraction may be induced by emotional stimuli and partially controlled by voluntary effort (Langworthy and Lewis, 1935).

The *physiological interpretation* of the findings in this case offers considerable material for speculation. The patient passed through a period of complete retention and incontinence with overflow to develop finally automatic micturition of considerable efficiency. When automatic micturition began, pains in the paralyzed portions of the body were first noticed, and were gradually associated in the patient's mind with the onset of voiding. They were always the pains of muscle cramp, and were associated with actual spasms of the paralyzed muscles. At the time the bladder first began to function automatically, its contraction was associated with severe pain in the urethra. If we accept an analogy with the pains which appeared later in the legs, we must assume that contraction of the muscle of the bladder or urethra produced this cramp-like pain. The sensory stimuli responsible for the contraction of the paralyzed striated muscle probably arose in the bladder wall at the time the vesical muscle was contracting. Stimuli from the hypalgesic skin surface also produced the same pattern of consequences. Stimulation of the soles of the feet when the patient stood and walked a few steps induced micturition. Also, micturition was elicited from the perineum, vagina or by pulling the pubic hairs.

Methods of controlling micturition had to do largely with pressure, closing the urethra. If the urine was held back, the bladder contractions subsided. Denny-Brown and Robertson have shown that closure of the external sphincter reflexly inhibits vesical contractions. Prevention of flexion of the toes was also partially successful in controlling vesical contractions.

The pathway by which sensation of impending micturition was carried to consciousness was not the usual one, since it was solely a feeling of muscle cramp in the urethra or legs. It probably must be assumed that the pain was carried along the intact fibers in the posterior columns of the cord. Perhaps we can conclude that the posterior columns normally subserve the painful sensation of muscle cramp.

It is possible now to follow the course of the reflex. The hyperirritable muscle of the bladder is overresponsive to stretch stimuli, and contracts forcefully when the viscus contains a small volume. Sensory stimuli are probably produced by these muscular contractions which activate the anterior horn cells controlling the striated muscle which is innervated by the sacral segments. This produces a violent contraction of the muscles. The sensory endings in the striated muscles are in turn overstimulated by this contraction, and the patient feels cramp-like pains due to impulses carried upward by the posterior columns of the spinal cord. Reflex micturition can be stimulated or controlled by manipulation of the paralyzed portion of the body. The bladder of this patient is undoubtedly released from control by portions of the nervous system above the lesion of the cord. The afferent ascending path is injured so that there is no longer normal vesical sensation. The efferent motor pathways from the brain are also involved.

OTHER EXAMPLES OF INVOLUNTARY MOVEMENTS OF THE LEGS ASSOCIATED WITH VESICAL DISTENTION

One of the most interesting features of this case is the spread of afferent stimuli from the bladder wall to produce contraction of the striated muscles of the legs. Authors have described vesical contractions produced by cutaneous stimulation, but the reverse picture of contraction of the striated muscle dependent on vesical contraction has been neglected. Recently we have studied micturition in many patients with injury of the central nervous system (Langworthy, Lewis, Dees and Hesser, 1936). One other similar case has been described by us (Langworthy, Lewis and Dees, 1936).

A white man, aged 51, was suffering from pseudo-bulbar palsy, and signs of bilateral injury of the cortico-spinal tracts. He was unable to walk or to speak plainly. The face was smooth and immobile. There was great difficulty in swallowing. The jaw jerk was active. Increased tone of a pattern typical of cortico-spinal tract injury was present in all four extremities. The deep reflexes were everywhere hyperactive. There were bilateral Hoffmann and Babinski reflexes, and bilateral ankle clonus. Examination of the bladder revealed that it had a capacity of only 40 to 50 cc., and the emptying contraction was precipitous and strong.

When the bladder was filled nearly to capacity, unusual responses were observed

in the legs. First it must be stated that no evidence of a so-called "mass reflex" could be elicited. On plantar stimulation of the soles of the feet, the movements of the toes were characteristic of a positive Babinski. Flexion at the ankle, knee and hip joints, such as is often associated with the marked development of the Babinski reflex, was slight. The patient was unable voluntarily to move the left leg, and movements of the right leg were very weak. With increasing bladder distention and just before the pressure rose to an emptying level, alternate flexor movements of both legs occurred of so violent a nature that the legs had to be restrained in order to obtain a record. These movements involved flexion at hip, knee and ankle. The toes, especially the great toes, were strongly flexed. These movements may be considered either as of the nature of Babinski reflexes elicited by sensory stimuli from the bladder wall or better, as manifestations of the sacral reflex.

In this patient bilateral, rhythmical contractions of the cremasteric muscles occurred during bladder filling, and increased in rate and amplitude when filling was nearly complete. These responses were seen in several patients with cortico-spinal tract injury, but they do not occur in the normal individual. Sensory impulses from the bladder apparently stimulate the anterior horn cells in the first lumbar segment of the cord which innervate the cremasteric muscles.

In the case of two patients with transverse lesions of the spinal cord it has been noticed that flexor movements of the legs developed and increased in amplitude with progressive distention of the bladder.

DISCUSSION

In either experimental or clinical observations concerning the mass reflex it is important now to study lesions confined to the lower lumbar or sacral regions. The reflex responses in these cases are not as complicated, and give further opportunity of analysis. The case cited here is an excellent example of release of the sacral reflex as described by Denny-Brown and Robertson. It differs from their description only in one regard. They describe the legs as abducted and externally rotated, whereas in the present example the legs were internally rotated. This difference is probably dependent on the level of the injury in the spinal cord and the muscles available for reflex activity.

SUMMARY

A young woman sustained an injury of the lower lumbar portion of the spinal cord. Reflex micturition finally became established.

Impending micturition produced flexion of the toes bilaterally, adduction of the right foot, extension and internal rotation of the legs. These movements were associated with cramp-like pain in the urethra and the contracted muscles. Holding the toes extended, postponed micturition. Voiding could be induced by stimulation of the perineal region. The contraction of the muscles illustrates the sacral reflex. Another example is given in which sensory impulses induced by vesical distention and contraction produced reflex contraction of the flexor muscles of the legs.

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CARDIAC ARRHYTHMIA AFTER BILATERAL URETERAL LIGATION IN THE DOG

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Suprarenalectomized dogs, which develop acute suprarenal insufficiency, frequently exhibit auricular fibrillation (1). There is also a marked increase in the plasma potassium concentration, blood nonprotein nitrogen and hemoconcentration. Since the intravenous injection of potassium salts produces in dogs certain alterations in the cardiac rhythm (1), the auricular fibrillation of suprarenalectomized dogs has been considered to be due to the increase in the plasma potassium concentration, even though the potassium is derived from an endogenous source. In order to determine whether an elevated plasma potassium concentration would produce the same effect in dogs with intact adrenal glands, both ureters of sixteen dogs were ligated, on the assumption—which proved to be true—that the plasma potassium concentration would rise as a result of the inability of the animals to excrete the products of progressive tissue catabolism.

PROCEDURE

Adult male and female mongrel dogs were used in the experiments. No food or water was allowed during the entire experiment. Control electrocardiograms with the dog lying on his back were made the day before operation. Thirty cubic centimeters of blood were removed from the femoral artery immediately before operation and divided into two equal parts, one of which was collected under oil without an anticoagulant, and the other mixed with heparin as recommended by Harrop and others (2).

After the blood had been obtained, a preliminary small dose of morphine was given. The animal was then anesthetized with ether and both ureters were ligated aseptically as close to the kidney pelves as possible.

After the operation the animals were watched closely in order to detect the first evidences of cardiac arrhythmia. As soon as abnormalities in the rhythm developed an electrocardiogram was made. If this did not show auricular fibrillation the experiment was continued. When auricular fibrillation appeared in the electrocardiogram a sample of blood was withdrawn for analysis and the animal was killed with ether. In order to be sure that the auricular fibrillation was not a terminal event, three dogs were not killed until more than two hours after the altered rhythm had appeared in their electrocardiograms. Autopsy was performed immediately after death in all experiments. A microscopic study was made of the heart and kidneys of two of the animals exhibiting auricular fibrillation.

The methods of analysis were as follows: Estimations of the plasma sodium were made by the method of Butler and Tuthill (3) using a trichloracetic acid filtrate instead of wet or dry ashing. The filtrate was prepared in the manner recommended by Kerr (4). This method in our hands was quite satisfactory, and the results compared favorably with those obtained by wet and dry ashing. The potassium determinations were also made on the trichloracetic acid filtrate of Kerr, by the method of Kramer and Tisdall, as described by Peters and Van Slyke (5). The carbon dioxide content was measured by the method of Van Slyke and Neill (5). The non-protein nitrogen determinations were made by the methods of Folin and Wu. The plasma chlorides were determined by the open Carius method as modified by Eisenman (5). All determinations were made in duplicate; abnormal results were checked in triplicate.

RESULTS

Approximately 36 hours after ureteral ligation the dogs developed weakness, spasticity of the hindlegs, an increased respiratory rate and in some instances bloody diarrhea and vomiting. When these symptoms appeared, the cardiac rhythm was rapid and regular. But as the symptoms progressed, tachycardia was usually replaced by marked bradycardia with a totally irregular cardiac rhythm. Neither coma nor convulsions were noted in any of the dogs.

Definite changes in the electrocardiograms were found in each of the twelve dogs. The most striking changes were bradycardia and

auricular fibrillation. The latter occurred in eight dogs and in only one of these was the ventricular rate more rapid than 50 per minute. Electrocardiographic records that showed an absence of the T-waves and a totally irregular ventricular rhythm were interpreted as auricular fibrillation (Fig. 1). Alterations in the T-waves of Leads II and

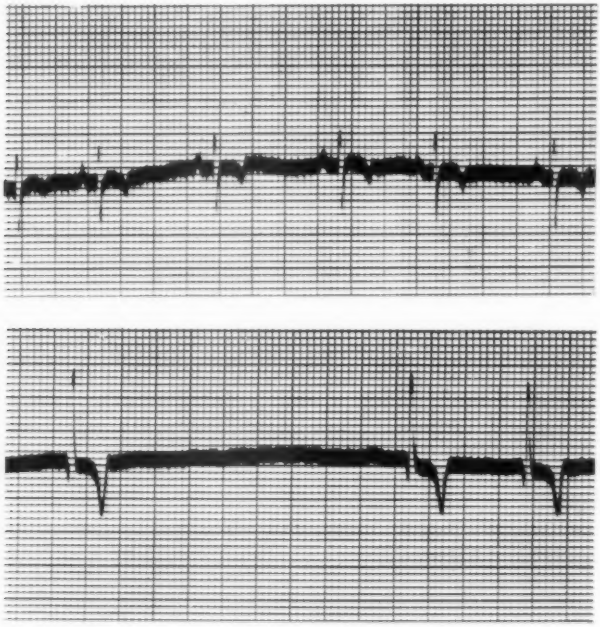

FIG. 1. ELECTROCARDIOGRAPHIC TRACINGS FROM DOG 4

The upper tracing, made before bilateral ureteral ligation, shows normal sinus rhythm. The lower tracing, made 53 hours after operation, shows slow, totally irregular ventricular rhythm and inverted T-waves of high amplitude. Both tracings were derived from Lead II.

III were observed in all tracings. The T-waves were sharp and of high amplitude, in some records as high as the QRS complexes. In addition the T-waves were frequently diphasic. There was no prolongation of the S-T segment. Tracings from normal control dogs showed none of these changes.

The chemical analyses of the blood showed fairly uniform results in all of the dogs (Table I). Atchley and Benedict (6) in 1927 demonstrated that there was frequently an increase in the plasma total base of dogs after ureteral ligation, but they did not make analyses for the sodium and potassium ions separately. The increase in total base, reported by them, was not as great as the combined increase in plasma sodium and potassium which is recorded in this report. In Table I it may be seen that the plasma sodium concentration did not change significantly except in dog 4 in which there was an increase of 13 milliequivalents per liter. In dog 7 the serum calcium was found to have increased from 11 mgm. per cent to 11.4 mgm. per cent. This could be accounted for by the slight hemoconcentration that occurred. The plasma potassium concentration increased considerably in every animal, and as a result of this increase there was a great decrease in the sodium:potassium ratio. In the control animals the average sodium:potassium ratio was 28.6; after operation the average ratio fell to 6.8. It is thought that the elevation in the total plasma base was compensated for by a rise in the phosphates and sulphates of the serum. The serum phosphate was greatly increased in the only two experiments in which this analysis was made. The blood nonprotein nitrogen was elevated in every dog.

The low carbon dioxide content of the serum shows that there was an acidosis in all of the dogs except no. 14. The plasma chloride concentration fell considerably in all of the dogs, and in one instance as much as 30 milliequivalents per liter were lost. The loss of chloride was due, in part, we believe, to vomiting and diarrhea; but in two dogs (nos. 3 and 5) that did not vomit or have diarrhea, there was nevertheless a loss of chlorides as great as in the other animals. This was also noted in the experiments reported by Atchley and Benedict (6), who were unable to account for the loss of chloride, even though they made analyses of the plasma, tissue, and vomitus. There was some hemoconcentration in all of the dogs, as is shown by a slight rise in the hematocrit and refractive index.

At autopsy the organs were entirely normal except for the kidneys, which showed a moderate distention of the kidney pelves. The urine contained in each kidney pelvis varied between 6 and 15 cc. Sections were made of the myocardium and kidney from two dogs. The

TABLE I

DOG	INTERVAL AFTER OPERATION	BLOOD ANALYSES								FINAL ELECTROCARDIOGRAM		
		Non-protein nitrogen	Sodium (plasma)	Potassium (plasma)	Na/K ratio	Chloride (plasma)	Carbon dioxide content (plasma)	Phosphate (serum)	Haematocrit	T-waves	Rate	Fibrillation
	hours	*mgm. per cent*	*m. eq./l.*	*m. eq./l.*		*m. eq./l.*	*m. eq./l.*	*mgm. per cent*				
Average control*		37	146.2	5.2	28.6	106.6	23.8	4.9	44			
3	48	190	144.2	23.1	6.2	83.2	15.8	—§	58	Sharp diphasic	42	Yes
4	53	190	144.0	25.4	5.6	97.4	14.0	13.6	44	Sharp upright diphasic	36	Yes
5	48	195	148.1	22.5	6.6	89.6	13.9	21.7	44	Sharp diphasic inverted	110	No
6	36	170	145.5	26.5	5.5	91.4	—	—	40	Sharp diphasic upright	50	Yes
7	52	260	150.4	21.3	7.0	97.2	14.3	—	43	Sharp diphasic	44	Yes
8†	72	310	149.8	21.7	6.9	77.4	—	—	55	Sharp diphasic	120	No
9	48	258	140.8	26.8	5.2	88.2	13.5	—	44	Sharp inverted	34	Yes
12	96	270	149.9	22.5	6.6	88.5	19.8	—	41	Sharp diphasic	20	Yes
14	24	188	158.5	17.6	9.0	76.8	21.8	—	43	Sharp diphasic	140	No
15‡	48	194	—	—	—	—	—	—	—	Sharp diphasic	110	Yes
17‡	54	210	151.2	16.8	9.0	84.5	16.7	—	40	Sharp diphasic	38	Yes
16	60	220	147.1	19.2	7.1	88.8	—	—	—	Sharp diphasic upright	130	No

* Average of chemical determinations before operation.

† Electrocardiogram was made 24 hours before blood was collected. When the blood was collected the rate was 30 and grossly irregular. An electrocardiogram could not be made at this time.

‡ Sodium chloride experiments.

§ Dash indicates that no determinations were made.

sections were prepared in the usual manner and stained with haemotoxylin and eosin. The kidneys showed some distention of the tubules. The sections of the heart showed that the myocardium was normal in every respect.

DISCUSSION

Under the conditions of these experiments there were many factors that might have entered into the physiological alterations that were observed. These conditions were: fasting, dehydration, a decrease in the plasma chloride concentration, a decrease in the plasma carbon dioxide content, an increase in blood non-protein nitrogen and serum phosphates, and a marked increase in the plasma potassium concentration. In addition there may have been an accumulation in the blood of substances for which chemical tests were not made because of the large amounts of blood which would have been required. One substance that might have been increased was the adenine nucleotide which Drury and Szent-Györgyi (7) have found to cause definite changes in the electrocardiogram when injected intravenously into the dog. These changes, however, were not comparable to the ones observed in the dogs reported here. Indeed, Drury and Szent-Györgyi succeeded in bringing about a reversion of auricular fibrillation to a normal rhythm by injecting adenine. We believe that this substance was not increased in the preparations used in this experiment, since Buell (8) has shown that the concentration of adenine is not elevated in human nephritis and closely follows the concentration of hemoglobin.

Lawson, Morgulis and Guenther (9) reported the electrocardiographic findings following prolonged fasting in the dog. None of their animals showed the changes that were found in ours after ureteral ligation. In our laboratory two dogs were fasted for a period of five days. Electrocardiographic tracings at the end of that time showed no abnormalities.

The calcium concentration of the blood serum of dog 7 showed an increase of 0.4 mgm. per cent. This slight rise which may be explained on the basis of hemoconcentration, would not account for the occurrence of auricular fibrillation in our dogs.

Increase in the blood non-protein nitrogen has been observed in

experimental nephritis in dogs, but auricular fibrillation has not been reported. No reports could be found in which electrocardiograms had been made. Streicher (10) was able to produce uremia in dogs by injecting intravenously a 20-per-cent solution of urea. No mention was made of any cardiac irregularity. To find out what the effect of a high concentration of urea in the blood of dogs would be on the rhythm of the heart, we injected urea into two dogs. The same experiment was performed on both animals and identical results were obtained. The ureters were left intact and 200 cc. of a 40-per-cent solution of urea were injected intravenously every day for three days. Electro-

TABLE II

DATE	NON-PROTEIN NITROGEN	SODIUM	POTASSIUM	CHLORIDE	CARBON DIOXIDE CONTENT	PHOSPHATE	REMARKS
	mgm. per cent	*m. eq./l.*	*m. eq./l.*	*m. eq./l.*	*m. eq./l.*	*mgm. per cent*	
12–18	38	143.1	5.6	105.0	24.4	4.6	Before injection
12–18	119	140.0	5.0	104.0	21.3		Immediately after 200 cc. of 40 per cent urea
12–19	210	142.3	5.3	99.4	19.4		One hour after 200 cc. of 40 per cent urea
12–20	335	144.6	4.9	99.7	22.0		Immediately after 200 cc. of 40 per cent urea
12–20	375	144.6	4.8	91.0	16.7	13.2	Two hours after 200 cc. of 40 per cent urea

Results obtained in dog 23 by intravenous injections of 40 per cent solution of urea. Dog 24 showed comparable results.

cardiograms made before and after each injection did not show auricular fibrillation. The blood non-protein nitrogen increased from a normal level of 38 milligrams per cent to 375 milligrams per cent at the end of the experiment in one dog (Table II). The only alteration that occurred in the electrocardiograms was an increase in the amplitude of the T-waves, which was comparable to that observed in the dogs whose ureters had been ligated. It is of interest to note that the plasma potassium concentration did not change significantly except perhaps to fall slightly. These experiments would indicate that the elevation in blood urea and the accompanying acidosis were not responsible for the auricular fibrillation noted in the ureteral ligation experiments. Inasmuch as the serum phosphate

also increased after the injection of urea, we believe that the foregoing remarks can be applied to that substance.

At the end of the urea experiment on dog 24, a 5-per-cent solution of ammonium chloride was given intravenously. The injection extended over a period of 45 minutes before the animal expired. A total of 50 cc. were given. The carbon dioxide content of the plasma, determined on arterial blood obtained 5 minutes before the death of the dog, was 16.3 milliequivalents per liter. Auricular fibrillation did not occur. Since this was performed in an animal with a greatly increased blood urea, it becomes evident that acidosis plus elevation in the blood non-protein nitrogen will not regularly produce auricular fibrillation.

In order to determine whether the altered rhythm, observed in the dogs after ureteral ligation, was a terminal event three dogs were allowed to live two or more hours after the electrocardiogram showing auricular fibrillation had been made.

It was also desirable to determine whether the heart would revert to a normal rhythm after auricular fibrillation had developed. This was tested in the following manner: dog 15, after auricular fibrillation had developed, was given 40 cc. of a 10 per cent solution of sodium chloride intravenously. An electrocardiogram made immediately after withdrawal of the needle from the vein showed normal sinus rhythm. The T-waves were still of high amplitude. In addition to the changes in the electrocardiogram there was a striking improvement in the appearance of the animal. The respirations, which, before the sodium chloride was given, were rapid and shallow, became quiet and regular after the injection. This experiment was repeated on dog 17 with the same results as noted above. In the latter experiment blood was collected for chemical analysis before the sodium chloride was injected and one hour after injection. The significant alterations were an increase in the plasma sodium concentration from 151.2 milliequivalents per liter to 155.0 milliequivalents per liter and a decrease in the plasma potassium concentration from 16.8 milliequivalents per liter to 12.4 milliequivalents per liter. The carbon dioxide content of the plasma increased by 2 milliequivalents per liter. The decrease in the plasma potassium concentration observed after the injection of sodium chloride was probably due to actual dilution of the ions by an increase in the blood volume, brought about by the

increase of sodium ions in the plasma. At any rate the sodium:potassium ratio was higher than before injection. The decrease in the plasma potassium concentration we believe was responsible for the reversion of the altered rhythm to a normal one.

Electrocardiograms were made on five dogs that died as a result of various experimental procedures. One was killed with ammonium chloride, two were killed with ether, another died from haemorrhage and one died with peritonitis and intestinal obstruction. Electrocardiographic tracings were obtained from all five dogs about two hours before death and in addition tracings were made on two of these dogs during the final moments of life so that the last contraction of the heart was recorded. None of these records showed auricular fibrillation. The plasma potassium concentration was not elevated in any of the dogs.

Low plasma chloride concentration was a constant feature in all of the dogs following ureteral ligation, but it is thought that this abnormality was not responsible for the bradycardia and auricular fibrillation, since it was shown in the experiments reported by one of us (1) that the plasma chloride concentration was normal or slightly elevated in the suprarenalectomized dogs that showed bradycardia and auricular fibrillation.

The alterations observed in the T-waves of Leads II and III can be explained by the fall in carbon dioxide tension of the blood, since those changes were observed by us after the injection of urea and ammonium chloride. Kountz and Hammouda (12), using the heart and lung preparations of dogs in perfusion experiments, showed that an increase in the CO_2 tension lowers the amplitude of the T-waves. Bradycardia and auricular fibrillation were not produced by this method. In humans, Barker and co-workers (13) have shown that an increased CO_2 tension produced an increase in the amplitude of the T-waves.

The effect of potassium salts on the heart, when injected intravenously into intact animals and in perfusion experiments on the isolated heart, has been described by numerous workers (1). The most constant effects were slowing of the heart rate, ventricular fibrillation and auricular fibrillation. It is thought that the alterations were produced by direct action on the myocardium rather than on the vagus nerve or the conduction system, since the results were obtained in the perfused heart as well as in the intact animal. McLean, Bay

and Hastings (11), in a series of experiments on the isolated rabbit heart, have estimated that, when the concentration of potassium in the perfusate reached a level of 12.3 milliequivalents per liter, ventricular fibrillation occurred.

Four of our dogs did not show auricular fibrillation in spite of an elevation in the plasma potassium concentration. The final blood samples and electrocardiograms in these experiments were obtained in the early evening and the animals were found dead the next morning. It is possible that if electrocardiographic tracings had been obtained later in the night these dogs would also have shown auricular fibrillation.[1] However, attention should be directed to the fact that, when the final electrocardiograms were made, some of these animals had a plasma potassium concentration which was just as high as that of several of the animals which developed auricular fibrillation. In a previous communication (1) reference was made to experiments which appeared to show that the occurrence of fibrillation in intact animals and in perfused hearts cannot be correlated exactly with the amount of potassium injected. It should not be expected, therefore, that auricular fibrillation would always occur at the same level of plasma potassium. Nevertheless, the following serial arrangement of the animals, according to the level of the plasma potassium, is instructive:

POTASSIUM	Na/K RATIO	AURICULAR FIBRILLATION
m. eq./l.		
26.8	5.2	+
26.5	5.5	+
25.4	5.6	+
23.1	6.2	+
22.5	6.6	+
22.5	6.6	−
21.7	6.9	−
21.3	7.0	+
19.2	7.1	−
17.6	9.0	−
16.8	9.0	+

[1] Dog 8 differed from the other three animals in this group in that the final electrocardiogram was made 24 hours before the final blood sample was collected. When the blood was collected the heart rate was 30 per minute and the rhythm was grossly irregular. Unfortunately, an electrocardiogram could not be made at this time.

From such an arrangement of the experiments it may be seen that auricular fibrillation occurred in all animals with a plasma potassium higher than 22.5 milliequivalents per liter. When the plasma potassium was between 16.8 and 22.5 milliequivalents per liter fibrillation occurred irregularly.

In all of the dogs of our series the plasma potassium concentration was over 16 milliequivalents per liter. In comparing the results obtained in the suprarenalectomized dogs, which developed suprarenal insufficiency and which also showed bradycardia and auricular fibrillation, with the results obtained in the dogs with bilateral ureteral ligation, we find that the electrocardiographic tracings were identical. Furthermore, in certain of the dogs the plasma electrolytes showed changes that were similar. It is our belief that the alterations in the rate and rhythm of the heart in the two conditions were due to similar changes in the electrolytes of the blood and tissues. The decisive change was, in all probability, the great increase in the plasma potassium concentration with a lowering of the sodium:potassium ratio.

Anuria in the human, when produced by obstructive lesions of the urinary tract, is comparable to the experimental conditions described in this communication. We have not had the opportunity to study a patient with anuria, but it is suggested that under these circumstances there might be a considerable elevation of the plasma potassium concentration and that auricular fibrillation might supervene in the final stages of the illness.

SUMMARY

1. An increase in the plasma potassium concentration was produced in dogs by ureteral ligation.

2. Slow auricular fibrillation and changes in the T-waves of the electrocardiogram occurred after bilateral ligation of the ureters in eight out of twelve experiments.

3. Reasons are advanced for the belief that the slow auricular fibrillation was caused by an increase in the plasma potassium concentration, with a lowering of the sodium:potassium ratio.

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ON THE SPECIFICITY OF THE THYREOTROPIC ACTION OF THE ANTERIOR PITUITARY GLAND[1]

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Since the discovery of the thyroid-stimulating action of the anterior pituitary gland in the course of the last decade relatively little investigation has been done to establish the specificity of this action for the anterior pituitary. Aron (1) found no thyreotropic effect in guinea pigs following the injection of extracts of muscle, kidney or testicle. P. E. Smith (2) determined that the substance acting on the thyroid to produce metamorphosis in the tadpole exists in the anterior but not in the posterior lobe of the pituitary. Loeser (3) was unable to find any storage of thyreotropic substance in the liver, spleen, adrenal or muscle of rabbits even after the administration of large amounts of the material intravenously.

On the other hand, certain workers have found thyroid-stimulating properties in organs other than the hypophysis. Schittenhelm and Eisler (4) claim to produce hyperplasia in the guinea pig thyroid by injection of portions of the mid-brain of cats. These were assayed to contain about one-third the activity of anterior pituitary extracts. These authors were able to obtain similar activity in the spinal fluid of cats but not in other areas of the brain and they suggest that the thyroid-activating substance is not actually formed in the mid brain but passes through it on its way from the pituitary to be liberated in the cerebrospinal fluid. Anselmino (5) describes thyroid hyperplasia with increased basal metabolic rate in rats following injections of ovarian tissue and follicular fluid, although crystalline oestrin had no such effect. He states that the thyroid-stimulating effect remains

[1] This investigation has been aided by a grant from the Josiah Macy, Jr. Foundation.

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after removal of the ovaries and uterus but disappears after hypophysectomy, and he concludes, therefore, that the ovarian substance injected must act on the thyroid by way of the pituitary. These findings seem to be contradicted, however, by the increased thyreotropic activity of the guinea pig pituitary which Loeser (6) was able to demonstrate after castration.

In 1935 Sturm and Schöning (7) announced that they had obtained definite thyreotropic activity from extracts of ovary, adrenal, pancreas and spleen made by the acetone precipitation method of Loeser (8). Indeed, the concentration of the substance in the ovary was found to be roughly equal to that in the anterior pituitary itself (one guinea pig unit in 0.05 to 0.001 mg.) and the total amount was far greater. The adrenals, likewise, produced stimulation of the thyroid in doses as low as 0.025 mg. of the Loeser extract. Pancreatic and splenic extracts gave a much less pronounced stimulation, while extracts of thyroid, parathyroid, pineal, liver and heart and skeletal muscle elicited no significant response. These authors postulate the theory that the pituitary does not itself secrete specific hormones but simply supplies directing impulses—presumably chemically mediated—which rearrange in a predetermined manner specific stimuli which it receives from other endocrine glands. They point out the close relationship between the thyroid and adrenals in maintaining the general body metabolism and between the ovaries and thyroid activity, as seen in pregnancy and menstruation, in an attempt to explain the thyreotropic effect of these two glands. They conclude that thyroid atrophy occurs after hypophysectomy because this tropic impulse of the hypophysis exerted on the glands under its control is gone and stimuli from one gland can no longer be redirected to act on another.

In view of the importance of these concepts and the startling experimental findings, it seemed advisable to attempt to repeat them. For this purpose alkaline extracts of beef ovaries were prepared by Loeser's (8) acetone precipitation method. Similar extracts of the anterior pituitary from the same cattle were prepared as controls. Six 200-gram guinea pigs were injected intraperitoneally daily for 4 days with amounts of the ovarian extract ranging from 25 mgs. to 100 mgs. Basal metabolic rates were recorded before and after the injection by

means of a Benedict closed-circuit apparatus, a base line being established by two or more determinations before the experiment was begun. The animals were killed 24 hours after the last injection; their thyroids removed immediately and examined histologically. In none of these animals was there any significant variation from the normal in the histological structure of the thyroid gland. Eight control animals were treated similarly with the anterior pituitary extracts prepared in the same way by Loeser's method and obtained from the same cattle in doses ranging from 0.05 to 15 mgs. All animals receiving over 2.5 mgs. showed marked histological evidence of thyroid stimulation.

In order to rule out the possibility of destruction of the thyreotropic substance during the process of extraction 4 guinea pigs were injected in a manner similar to that employed for the first group with an aqueous suspension of acetone-desiccated powdered beef ovaries in amounts varying from 25 to 150 mgs. of the dry powder. None of these animals gave the slightest histological evidence of thyroid hyperplasia, whereas six control guinea pigs given an aqueous suspension of from 5 to 100 mgs. of acetone-desiccated anterior pituitary powder all showed definite hyperplasia varying in degree from slight to marked depending directly on the size of the dose. It is of interest to note in passing that the amount of stimulation caused by 5 mgs. of crude anterior pituitary powder in this simple aqueous suspension approximated closely to that obtained with 2.5 mgs. of the highly purified alkaline extract giving a yield of only 5 per cent of the crude acetone-dried powder. Table 1 and figures A, B, C and D of plate I demonstrate the relative thyreotropic effect of these four types of extracts.

Owing to the difficulty of obtaining consistent basal metabolic rates in small animals, the individual values in this table show considerable variation. Taking each group as a whole, however, the figures assume greater significance. The three guinea pigs receiving over 2.5 mgs. of purified anterior pituitary extract showed an average increase of 33 per cent over their original basal metabolic rate and the three animals given over 25 mgs. of crude anterior pituitary powder likewise showed a rise of 22 per cent. On the other hand, the average rise in the 10 animals in the two groups receiving ovarian substance was only 7 per cent, a figure well within the range of normal variation. The final

arbiter of thyroid stimulation, the histological appearance of the gland, will be demonstrated in the microphotographs to follow.

TABLE 1

Comparison of effect of daily injection of beef anterior pituitary and ovarian extracts on the thyroid gland of the guinea pig

GUINEA PIG	TYPE OF EXTRACT	AVERAGE DOSE PER DAY	NUMBER OF DAYS	WEIGHT		BMR (cc. O_2/sq. m./min.)		DEGREE OF THYROID HYPERPLASIA (0–++++)
				Beginning	End	Beginning	End	
		mg.						
6 II	Purified ant. pit. ext.	15	4	226	202	104	148	++++
7 II	"	15	4	262	231	104	137	++++
9 II	"	5	4	219	208	103	135	+++
11 I	"	2.5	4	182	178	106	139	+
11 II	"	1	4	234	245	110	121	±
11 IV	"	0.1	4	195	194	112	119	0
6 I	Purified ovarian ext.	45	4	230	197	111	123	0
7 I	"	90	4	234	216	101	111	0
9 I	"	100	4	218	195	110	120	0
22 II	"	25	4	202	187	115	108	0
22 III	"	75	4	226	180*	117	126*	0
22 IV	"	25	4	224	189	117	112	0
16 I	Crude dried ant. pit. powder	100	4	271	228	106	114	++++
16 II	"	50	4	231	211	92	138	++++
16 III	"	25	4	232	213	120	131	++++
18 I A	"	15	4					+++
18 II A	"	10	4					+++
18 III A	"	5	4					+
20 I	Crude dried ovarian powder	150	4	272	234	104	126	0
20 III	"	100	4	252	221	106	113	0
20 II	"	50	4	231	223	98	104	0
20 IV	"	25	4	217	207	108	98	0

* These figures were obtained on the day after the second injection. This animal died of peritonitis on the day after the fourth injection. The thyroid, however, showed no hyperplasia.

One obstacle to the complete acceptance of the specificity of the thyreotropic hormone for the anterior pituitary has been the difficulty of demonstrating the thyreotropic activity of the pituitary in homol-

ogous species, at least as far as the guinea pig is concerned. Loeb and Bassett (9), Seibert and Smith (10) and Loeser (4) have found little or no effect on the guinea pig thyroid produced by daily implantation of the pituitaries of other guinea pigs. Collip (11) uses this fact as an illustration of his theory of inverse response: "The responsiveness of an individual to administered hormone varies inversely with the hormone content or production of the individual's own gland." It seems possible that one reason for the lack of response to guinea pig pituitary may be the relatively small doses employed by previous workers. Accordingly, an attempt has been made to employ doses of acetone-

TABLE 2

Effect of injection of guinea pig anterior pituitary on the thyroid of the guinea pig

GUINEA PIG	AVERAGE DOSE OF GUINEA PIG ANTERIOR PITUITARY POWDER PER DAY	NUMBER OF DAYS	WEIGHT		BMR (cc. O_2/sq.m./min.)		DEGREE OF THYROID HYPERPLASIA (O–++++)
			Beginning	End	Beginning	End	
	mg.						
19 I	15	27	212	274	103	136	++
19 II	15	4	180	170	105	134	+
19 III	15	17	200	196	106	126	++
19 IV	10	4	174	136	107	150*	++
30 I	40	4	228	225	93	102	+++

* This animal had a severe plastic peritonitis which may account for the unusually high oxygen consumption. It is included in the series, however, because in control animals a similar degree of peritonitis produced by non-hypophyseal substances gave rise to no thyroid stimulation.

dried guinea pig pituitary powder equivalent weight for weight to those of a similarly prepared beef anterior pituitary powder known to be effective.

Table 2 shows clearly that the guinea pig's own anterior pituitary contains definite amounts of thyreotropic substance. If sufficiently large amounts are given or if the administration is continued long enough, marked thyroid stimulation occurs in the homologous species. Here, too, in spite of the individual variations of different animals, we have corroborative evidence of stimulation in the average increase in basal metabolic rate of 23 per cent when the group is taken as a whole (animal 19 III not included). When one considers, however, that in

order to obtain the most marked stimulation (as in animal 30 I) daily injections of 40 mgs. of the guinea pig anterior pituitary powder, or approximately 30 glands, are required, it is obvious that both the relative and absolute amounts of thyroid-stimulating substance in the guinea pig pituitary is extremely small. A comparison of table 2 with table 1 reveals the fact that the absolute concentration of thyreotropic substance in the beef anterior pituitary, as evidenced by the histological appearance of the thyroid of the test animal, is definitely greater than that in the anterior pituitary of the guinea pig.

These differences in the degree of thyroid hyperplasia may be seen in the microphotographs of plate I. Attempts to increase the concentration of the thyreotropic substance in the hypophysis of the guinea pig by castration and by thyroidectomy have so far been unsuccessful in our hands.

DISCUSSION

It would seem from the above investigation of ovarian extracts that there is no evidence of any thyroid-stimulating property inherent in whole ovarian tissue. Further confirmation of the above findings comes from the recent work of Ballif and Gherscovici (12) who likewise repeated the experiments of Sturm and Schöning with similar negative results.[3]

The fact that definite thyroid stimulation can be obtained from the guinea pig anterior pituitary, if sufficient amounts are administered, appears to be one more link in the chain of evidence in favor of the specificity of this activity of the anterior pituitary gland.

SUMMARY

1. Extracts of beef ovary, purified by Loeser's method, produce no changes in the thyroid gland of the guinea pig, whereas similar extracts of the anterior pituitaries of the same animals cause good thyroid stimulation. The same holds true for the crude acetone-desiccated powder made from these two glands.

[3] Since this work was done, D. A. McGinty and N. B. McCullough (*Proc. Soc. Exper. Biol. and Med.*, **35**, 24, 1936 (October), have also reported failure to obtain thyreotropic activity from extracts of beef, sheep and hog ovaries made by Loesser's method.

2. Guinea pig anterior pituitary powder produces definite stimulation in the guinea pig thyroid, if given in sufficiently large amounts or over a long enough period of time. The absolute concentration of thyreotropic substance is definitely less in guinea pig than in beef anterior pituitary.

I wish to express my sincere thanks to Dr. E. K. Marshall, Jr. for suggesting the problem and for his advice and encouragement during the course of the investigation.

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PLATE

PLATE I

(× 100 H & E)

FIG. A. Guinea pig 9 II. Purified anterior pituitary extract—5 mgs. daily for 4 days.

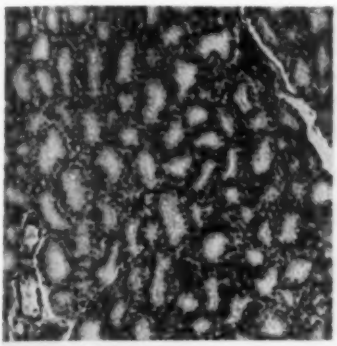
FIG. B. Guinea pig 6 I. Purified ovarian extract—100 mgs. daily for 4 days.

FIG. C. Guinea pig 16 III. Crude acetone-dried anterior pituitary powder—25 mgs. daily for 4 days.

FIG. D. Guinea pig 20 I. Crude acetone-dried ovarian powder—150 mgs. daily for 4 days.

FIG. E. Guinea pig 19 I. Acetone-dried guinea pig anterior pituitary powder—15 mgs. daily for 27 days.

FIG. F. Guinea pig 30 I. Acetone-dried guinea pig pituitary powder—40 mgs. daily for 4 days.



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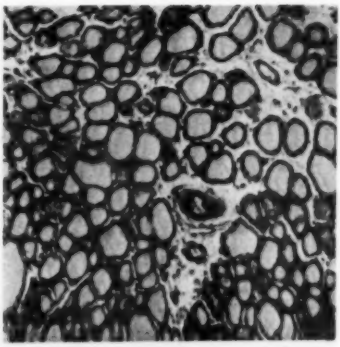

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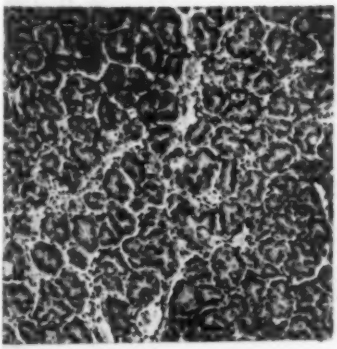

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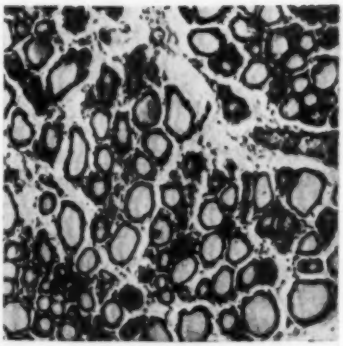

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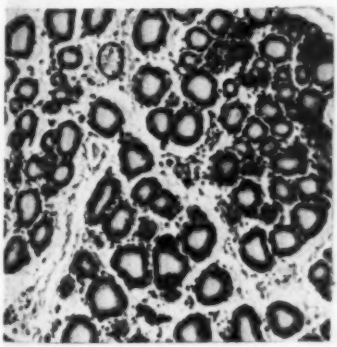

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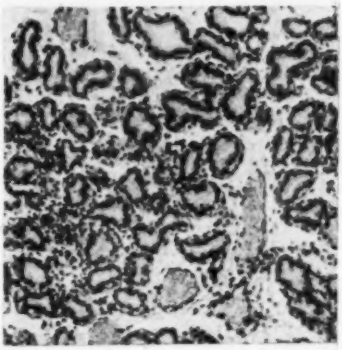

F

THE USE OF A MUSCLE PEDICLE FLAP FOR PREVENTION OF SWELLING OF THE ARM FOLLOWING THE RADICAL OPERATION FOR CARCINOMA OF THE BREAST

Preliminary Report

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Swelling of the arm on the operated side is present to a greater or lesser degree in all patients upon whom the radical operation for carcinoma of the breast has been performed. Indeed, in many patients this postoperative oedema may be so slight that, unless the arm, forearm and hand, are most carefully inspected and measured, this sequel to the operation may be entirely overlooked, not only by the surgical attendant but even by the patient. If, however, pre- and postoperative measurements are carefully recorded in addition to subjective and objective observations on the part of the patient and surgical staff, some degree of swelling of the arm will be recorded in all cases. This may be limited to a mere puffiness of the fingers or the obliteration of a few wrinkles in the hand. In some, however, the enlargement reaches distressing proportions, causing great physical as well as mental suffering. In a few recorded instances this postoperative swelling has been so intense as to necessitate amputation of the affected arm. In many it has been the source of great embarrassment not only because of its unsightly appearance but also because of an almost total loss of function of the arm. The primary factor in the production of this lymphoedema of the arm is the interruption of the lymphatic pathway due to the removal of the axillary lymphatic vessels and glands associated with the removal of the perineural and perivascular tissue of the subclavicular and axillary regions. Probably, as Halsted (1) pointed out, the secondary factor is the presence of infection in the skin or the dead space that is left between the axillary structures and the overlying skin flaps upon completion of the operation. This dead space is smallest, when the upper skin fold is sewn to the chest wall so as to intimately embrace the axillary vessels, as in the closure described by Halsted (1), in which an Ollier-Thiersch graft is employed to supplant the resulting skin defect, and greatest, when the upper lateral skin flap is stretched or tented over the axillary region under tension in order to approximate the medial skin edge for closure. As a result an inverted triangular empty space is formed, and in its apex run the axillary artery and vein. This space is obliterated first by serum and later by granulation tissue which results in an abundant formation of stenosing cicatrix.

Due to the fact that sloughing of the skin margins is present to some degree in any type of closed plastic operation, infection readily spreads in the skin lymphatics and to the axillary dead space. However, in many instances in which the method of obliteration of this axillary dead space by the Halsted operative method was meticulously carried out, and despite the fact that there was absolutely no evidence of infection, nevertheless at various intervals after operation a very pronounced and annoying swelling of the arm would occur. It would seem that the capacity of individuals to develop a collateral lymphatic circulation varies considerably.

Primarily, with the intention of aiding the reestablishment of the lymphatic flow from the arm after operation, and secondarily, to accomplish an immediate and more complete obliteration of the axillary dead space, thus minimizing the occurrence of secondary infection, a muscle pedicle flap has been employed. A fan-shaped design of muscle of suitable proportions is cut out of the latissimus dorsi so as to include the subscapular nerve, artery, and vein, the free edge of the muscle being utilized to form the future upper margin of the pedicle flap. After sufficient width has been obtained to completely cover the axillary structures and fill the infraclavicular dead space, the latissimus dorsi is split along the course of its fibres towards and up to within a few centimeters of its insertion. The muscle flap, when correctly cut, will fit without tension, and on relaxation will fill the axillary dead space. The edges of the flap should be sutured with interrupted fine silk sutures to the remaining remnants of the origin of the pectoralis major from the clavicle and the sternum and also to the internal and external intercostal muscles of the first and second interspaces. The nicety with which this muscle pedicle flap fits the axillary space without tension or torsion is very gratifying. A muscle bridge with its lymphatic channels is thus established from the arm to the thorax. Reichert (2) in 1931 demonstrated that a regeneration of lymphatic vessels would occur following muscle suture. A regeneration of the lymphatic channels between the sutured ends of the latissimus dorsi pedicle flap and the stumps of origin of the pectoralis major probably occurs. Further connection between the lymph channels of the chest wall and the remaining axillary areolae with those of the pedicle flap is probably established. The latissimus dorsi muscle was chosen because it would not be contaminated with carcinoma and also on account of its anatomical position. The blood and nerve supply of the flap should be preserved to prevent subsequent atrophy of the muscle. The dissection and suturing of this flap can be done in less than ten minutes, so that it does not prolong the main operation. Although the removal of skin sufficient to necessitate skin grafting as a method of closure is to be preferred, the use of the muscle pedicle flap will tend also to reduce the hazard of axillary complications so common in the plastic method of skin closure of the wound.

The operative procedure described above has been utilized thus far in the treatment of four cases of carcinoma of the breast. In each of these the wound healed perfectly and there was no subsequent swelling or interference with the

movements of the arm. The operations were performed approximately 2 years, 1 year, 6 months and 6 weeks ago, respectively.

The employment of a muscle pedicle flap is suggested for the relief of lymphoedema elsewhere, especially of the leg, and at the present time is being employed in the first case for the relief of idiopathic elephantiasis of one leg. The principle of a muscle pedicle flap bridge to divert the flow of lymph through the new channels is one that may prove useful in other similar lymphatic obstructions.

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A NEW OPERATIVE TECHNIQUE FOR CLOSURE OF THE MAIN BRONCHUS

Preliminary Report

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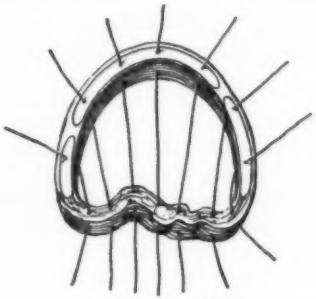
Submitted for publication April 19, 1937

From experience in the closure of the primary bronchus during the operation of total pneumonectomy in a series of 23 patients over a period of three years has been developed a simple and most satisfactory method of bringing about occlusion, which has been employed in five consecutive cases, successfully. The bronchus, whether it be the right or the left, is cut across in the mediastinum near the bifurcation of the trachea. The incision is made slightly oblique to the long axis of the bronchus, on a line running from above and lateral to below and medial. The cut edge of the stump forms an angle of about 45 degrees with the superior border of the primary bronchus and about 135 degrees with its inferior medial border. In addition to the slanting direction of the incision across the bronchus, the cut is made on the bias so that the posterior membranous portion is a trifle longer than the more anterior cartilaginous wall. Interrupted fine "a" silk sutures are then placed in the membranous portion in such a way that the needle does not penetrate the lumen (fig. 1a), but picks up a portion of the tissue a few millimeters proximal to the cut edge. The needle is then inserted into the cut edge of the cartilaginous ring of the bronchus directly opposite (fig. 1a), including only the tissues that are external to the mucous membrane. From ten to twelve of these sutures are laid in a fan-shaped pattern. Thus, when the knots are pulled home, the relaxed and tough posterior membranous wall is not only at all points snugly applied or fitted to the inner surface of the semicircular cartilaginous ring (fig. 1b), but also, as a result of the way in which the sutures have been placed, the membranous portion is rolled over the cartilaginous cut edge in a way corresponding to the inversion of the intestinal wall (fig. 2). The cut ends of the mucous membrane are thus approximated on the inside of the blind end stump. This method of closure of the cut end tends to flatten out the horse-shoe-shaped bronchial cartilage rather than constrict it, and therefore puts no tension whatever upon the suture line. Two parallel rows of through and through mattress sutures are placed proximal to the above mentioned interrupted row. They are separated from the end and from each other by the width of one cartilaginous ring. The suture passes completely through the bronchial walls including the cartilaginous rings. These proximal sutures consist of no. 1 chromic catgut. Additional rows of these interrupted mattress sutures may be employed, whenever necessary. One row contains about eight sutures.

The posterior membranous portion of the bronchus is, in the human, amply abundant to line, as it were, the entire semicircle of the cartilaginous ring, and in addition stretches very easily. Occasionally on the left it may be helpful to leave a slight bit more of the under-lip of the membranous portion so as to curl back over



1a

1b

2

FIGS. 1*a*, 1*b*, AND 2

the cut end. The membranous wall of the bronchus is abundantly supplied by the bronchial artery.

A fact of some importance may be added. By the use of an oblique incision and a similar technique of closure, an adjacent portion of the trachea may be removed together with the involved bronchus, thus enabling the operator to deal with tumors extending as far as the carina or involving one wall of the trachea along its lateral margins.

BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of this Journal.)

Urological Roentgenology. By MILEY B. WESSON and HOWARD E. RUGGLES. 269 pp. Illus. $5.00. (*Lea & Febiger, Philadelphia, 1936.*)

This small volume of 269 pages contains illustrations and descriptions of the more common and the rare lesions of the kidneys, ureters and bladder, as shown by x-ray studies. The illustrations of plain x-ray films, intravenous pyelography, retrograde pyelography, cystography and bone films for metastases are excellent. The index is complete. The description of technique is very brief. We regret that the value of stereoscopy has not been emphasized by the authors.

This volume is recommended to the urologist as a well illustrated reference book. It will prove useful to the interne in urology and roentgenology and to any practitioner or student who wishes to learn the interpretation of urograms.

L. G. L.

Eugenical Sterilization. By The American Neurological Association Committee for the Investigation of Eugenical Sterilization. 211 pp. $3.00. (*The Macmillan Company, New York, 1936.*)

This book of some 200 pages gives a thoughtful and painstaking review concerning the scientific background of sterilization in this country and abroad. Preceding the recommendations of the Committee are informative chapters dealing with the legal aspects of sterilization in this country, the main arguments for sterilization, and studies on the hereditary aspects of mental and neurological disease processes. This Committee, appointed by The American Neurological Association, goes on record as favoring permissive rather than compulsory legislation on sterilization matters. An excellent bibliography is contained in this publication.

This book should be of value, especially at this period of the year when legislatures are in session with sterilization as an annual topic for agitation.

E. L. R.

Applied Dietetics for Adults and Children in Health and Disease. By SANFORD BLUM, M.D. Pp. 408. $4.75. (*F. A. Davis Company, Philadelphia, 1936.*)

A compendium of diets for adults and children in health as well as in disease. "Type meals" (including lists of permitted and forbidden foods) are given for each and every disease, simple or complicated.

In the introduction the author stresses the value of individualizing diets in order to give one which can and will be followed.

The book has been divided into two parts. Part 1 deals with "Dietary for Adults in Health and Disease," Part II gives "Dietary for Infants and Children in Health and Disease." This latter division includes, under Section A, "Feeding During the First Year," Feeding During the Second Year." Section B summarizes "Diet for Children in Disease."

A practical table of the vitamin value of the more common food substances is given at the end of the book.

J. W.

Exophthalmic Goiter and Its Medical Treatment. By ISRAEL BRAM, M.D. Second Edition. 456 pp. Illus. $6.00. (*The C. V. Mosby Company, St. Louis, 1936.*)

Much of the recent work on thyroid physiology and pathological physiology is discussed in this book. The author is still an ardent believer in "a rational medical régime as the *sole* treatment" of exophthalmic goiter, and since he is the one vocal champion of this point of view, his book is interesting. However, his comments on the physiology and pathology of the thyroid gland are those of a therapeutist of goiter cases.

The Bram Quinine Test reveals an abnormal tolerance to quinine in cases of hyperthyroidism and is, according to the author, "as dependable as the B.M.R. and as accurate a guide in treatment." Since time need not be considered in Dr. Bram's method of treating hyperthyroidism, it matters little that this test requires two or three weeks for its completion.

Of 5,000 sufferers from Graves' disease treated medically, 2,600 were followed up after from 3 to 20 years. Of these 90% were perfectly well, 4% suffered only from slight exophthalmos, and 6% from slight hypothyroidism, exophthalmos and enlarged heart. "Recovery" occurred in early cases after only several weeks' treatment, in late cases up to 18 months, and in cases of average severity after from four to ten months.

The principles of medical treatment are discussed under "(a) removal of discoverable infectious foci, (b) a varying rest program to overcome and repair the ravages of the hyperactive 'kinetic drive,' (c) a properly outlined diet, (d) the use of medicaments [Quinine evidently is the author's favorite drug and he vigorously warns against the injudicious use of iodine.] in efforts to eliminate the results of the various vicious circles, and (e) the application of psychotherapy, not alone for its value in the interests of the recovery of the patient, but also for its influence on the immunizing mechanism of the individual in efforts at *permanency* of recovery."

". . . .; briefly, it is the deficiency or absence of rationalization that has caused the patient's plight, and the correction thereof is the means of recovery. Merely an attack on the "lump on the neck," while at times palliative and in many ways persuasive, is inconclusive."

The Bram mortality rate of cases "for which primarily the responsibility was

accepted" in 3,924 cases was 0.3%. This, a most important part of the book, is briefly reported in one page.

Even if one disagrees with the author's main thesis one may still find much of interest in this book and the chapter on eye symptoms is excellent and there are many important references.

H. M. T., Jr.

Handbook of Ocular Therapeutics. By Sanford R. Gifford. 2nd ed. 341 pp. Illus. $3.75. (*Lea & Febiger, Philadelphia, 1937.*)

In this new (second) edition of Gifford's excellent "Ocular Therapeutics" revisions and additions account for an increase of seventy pages of text. Some of the illustrations in the first edition were not too good, but this defect has been remedied. A commendable change in the general construction of the book is the use of italic type which serves to focus the reader's attention on essential details.

A few conditions formerly omitted are dealt with in this edition. New material has been carefully chosen. Summaries of the use of vitamins, tissue extracts, medical diathermy, and a chapter on diseases of the orbit, are among the useful additional material.

F. B. W.

Laboratory Outline in Filterable Viruses. By Roscoe R. Hyde. 85 pp. $1.50. (*The Macmillan Company, New York, 1937.*)

Most laboratory instructors prefer to make their own outlines of the work to be done, since so much depends on what apparatus and material are available. However, the present volume should be useful as a guide to a teacher in planning a laboratory course in filterable viruses. Furthermore, it contains information, such as the two pages given over to the calculation of pore diameters from Poiseuille's Law, which would be invaluable to the student.

E. A. B.

An Introduction to Comparative Biochemistry. By Ernest Baldwin. 112 pp. $1.50. (*Cambridge; The University Press. New York: The Macmillan Company, 1937.*)

The little book of one hundred pages by Ernest Baldwin (Fellow of St. John's College, Cambridge, England) entitled "An Introduction to Comparative Biochemistry" tells a dramatic story which affords entertaining reading. It describes in non-technical language numerous biochemical facts, many of which have been discovered within the past decade, with the purpose of helping to elucidate evolution and heredity. Interpretations are, of course, controversial. Although the pertinence of biochemistry in this connection has long been recognized, perhaps the unique value of this book lies in the author's critical use of the modern biochemical, in contrast to the usual anatomical, approach to the study of these problems. This point of view, in turn, may give to the investigator a more fundamental conception of many problems of physiology and medicine.

M. V. B.